Understanding the relationship between vaccination, vaccine-preventable diseases, and HIV infection among sub-Saharan African children

by

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Declaration

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Abstract

Numerous care and treatment guidelines pinpoint vaccination as a crucial preventive strategy for HIV-infected patients, but data regarding these vaccines among children living with HIV are still very scanty. There are knowledge gaps concerning the understanding of the mediators of vaccine protection, adverse effects and fundamental aspects of the epidemiology of various vaccine-preventable diseases. Likewise, there is also limited information on the determinants of vaccine non-uptake within the HIV-infected population, and on the association between maternal HIV status and the vaccination status of her HIV-exposed child. Further synthesis of all available evidence is required to provide reliable and easily accessible information for decision-makers and healthcare workers. We completed evidence synthesis of existing studies and secondary analyses of existing data sets using different research methods such as systematic review, meta-analysis, meta-regression and multivariable logistic regression models.

We found that the burden of vaccine-preventable diseases is still high among HIV-infected and HIV-exposed children in sub-Saharan Africa. Several routine vaccines show possibilities for direct and indirect protection against various vaccine-preventable diseases among HIV-infected and HIV-exposed children. However, HIV-infected children are less likely to be protected against vaccine-preventable diseases when compared to non-exposed children. There is no significant difference in the uptake of the full series of three doses of diphtheria-tetanus-pertussis containing vaccines (DTP3) among infants of HIV-infected mothers and those of uninfected mothers in sub-Saharan Africa. Vaccination coverage for both HIV-exposed children and non-exposed children is still sub-optimal.

Furthermore, individual and contextual factors such as maternal age, educational level, unemployment, and adult literacy level contributed significantly to non-uptake of DTP3 among the children of HIV-infected women across sub-Saharan Africa. The symptoms of acute respiratory infections show no statistical difference in the overall estimates between the children of HIV-infected mothers who were vaccinated with DTP3 and the ones who were not vaccinated. The data for episodes of diarrhoea were pooled together with resultant nil significant difference in the overall estimates between the children of HIV-infected mothers who were vaccinated with DTP3 and those not vaccinated. Many African countries also recorded high rates of respiratory

infections and diarrhoeal diseases among both HIV-exposed and unexposed children. Residency in communities with high unemployment was an independent predictor of acute respiratory infections among immunised and HIV-exposed children while those born to women aged 15-24 or 25-34 years old were significantly more likely to develop diarrhoeal diseases.

There is a need to address sub-optimal uptake of vaccines among HIV-exposed and non-exposed children. Epidemiological studies on vaccine-preventable diseases and the development of more efficacious vaccines are required for vaccine-preventable diseases studies with respect to HIV-infected and HIV-exposed uninfected children. The findings of this research would be useful in advocating for a more equitable share of healthcare resources especially for preventive services such as vaccination of both HIV-exposed and non-exposed children with subsequent reduction in the burden of vaccine-preventable diseases.

Opsomming

Verskeie sorg- en behandelingsriglyne dui op inenting as ’n noodsaaklike voorkomingstrategie vir MIV-positiewe pasiënte. Tog is daar nog weinig data beskikbaar oor hierdie inentings onder kinders wat met MIV leef. Daar bestaan kennisleemtes in die begrip van die bemiddelaars van inentingsbeskerming, die nadelige gevolge van inenting, en fundamentele aspekte van die epidemiologie van verskeie siektes wat met inentings voorkom kan word. Eweneens is daar beperkte inligting oor die redes waarom die MIV-positiewe populasie nié van inenting gebruik maak nie, en die verband tussen die ma se MIV-status en die inentingstatus van haar MIV-blootgestelde kind. Verdere sintese van alle beskikbare bewyse word vereis om betroubare en maklik toeganklike inligting aan besluitnemers en gesondheidsorgwerkers te voorsien. In hierdie navorsing is die bewyse uit bestaande studies gesintetiseer en sekondêre ontledings van die bestaande datastelle onderneem. Hiervoor is verskillende navorsingsmetodes gebruik, waaronder stelselmatige oorsig, meta-ontleding, meta-regressie en meerveranderlike logistiese regressie.

Die ontledings toon dat die las van inentingsvoorkombare siektes steeds hoog is onder MIV-positiewe én -blootgestelde kinders in Afrika suid van die Sahara. ’n Aantal roetine-inentings blyk MIV-positiewe en -blootgestelde kinders moontlike direkte sowel as indirekte beskerming teen ’n verskeidenheid inentingsvoorkombare siektes te bied. Tog is die waarskynlikheid dat MIV-positiewe kinders teen inentingsvoorkombare siektes ingeënt sal word kleiner as by nieblootgestelde kinders. Daar is geen beduidende verskil tussen die gebruik van die volle reeks van drie dosisse difterie-tetanus-pertussis-inentings (DTP3) onder die babas van MIV-positiewe ma’s en die babas van MIV-negatiewe ma’s in Afrika suid van die Sahara nie. Nietemin is inentingsdekking vir sowel MIV-blootgestelde as -nieblootgestelde kinders steeds suboptimaal.

Daarbenewens het individuele en kontekstuele faktore, soos die ma se ouderdom, opvoedingsvlak, werkstatus en geletterdheidsvlak, ’n aansienlike invloed op die niegebruik van DTP3 onder die kinders van MIV-positiewe vroue in Afrika suid van die Sahara. Die simptome van akute respiratoriese infeksies toon geen statistiese verskil in algehele ramings tussen MIV-positiewe ma’s se kinders wat met DTP3 ingeënt is en kinders wat nié ingeënt is nie. Die data vir gevalle

van diarree is saamgevoeg, en dui ook op geen beduidende verskil in algehele ramings tussen MIV-positiewe ma's se kinders mét DTP3-inenting en diegene sónder sodanige inenting nie. Baie Afrikalande meld 'n hoë voorkoms van respiratoriese infeksies en diarreesiektes onder sowel MIV-blootgestelde as -nieblootgestelde kinders aan. Verblyf in gemeenskappe met hoë werkloosheidsyfers is 'n onafhanklike voorspeller van akute respiratoriese infeksies onder geïmmuniseerde en MIV-blootgestelde kinders, terwyl die kinders van vroue in die ouderdomskategorie 15–24 of 25–34 'n aansienlik groter geneigdheid tot diarreesiektes toon.

Die suboptimale gebruik van inentings onder MIV-blootgestelde en -nieblootgestelde kinders verg aandag. Meer studies oor inentingsvoorkombare siektes by MIV-positiewe en MIV-blootgestelde dog -negatiewe kinders word vereis met betrekking tot epidemiologie sowel as die ontwikkeling van doeltreffender entstowwe. Die bevindinge van hierdie navorsing sal nuttig wees om voorspraak te doen vir 'n billike toewysing van gesondheidsorghulpbronne aan voorkomende dienste, waaronder die inenting van sowel MIV-blootgestelde as -nieblootgestelde kinders, wat die las van inentingsvoorkombare siektes sal verlig.

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List of publications and completed studies

1. **Adetokunboh OO**, Awotiwon A, Ndwandwe D, Uthman OA, Wiysonge CS. The burden of vaccine-preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa: a systematic review and meta-analysis.
   Status: Submitted for publication

2. **Adetokunboh OO**, Ndwandwe D, Awotiwon A, Uthman OA, Wiysonge CS. Systematic review and meta-analysis of evidence related to vaccine efficacy and effectiveness among HIV–infected, HIV-exposed uninfected and HIV-uninfected children.
   Status: Submitted for publication

3. **Adetokunboh OO**, Uthman OA, Wiysonge CS. Effect of maternal HIV status on vaccination coverage among sub-Saharan African children: a socio-ecological analysis. *Human vaccines & immunotherapeutics*. 2018; May 22;14(10):2373-81.
   Status: Published

4. **Adetokunboh OO**, Uthman OA, Wiysonge CS. Non-uptake of childhood vaccination among the children of HIV-infected mothers in sub-Saharan Africa: A multilevel analysis. *Human vaccines & immunotherapeutics*. 2018 Oct 3;14(10):2405-13.
   Status: Published

5. **Adetokunboh OO**, Uthman OA, Wiysonge CS. Morbidity benefit conferred by childhood immunisation in relation to maternal HIV status: a meta-analysis of demographic and health surveys. *Human vaccines & immunotherapeutics*. 2018 Oct 3;14(10):2414-26.
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6. **Adetokunboh OO**, Uthman OA, Wiysonge CS. Non-specific effects of childhood vaccines on acute childhood morbidity among HIV-exposed children in sub-Saharan Africa: a multilevel analysis. *Human vaccines & immunotherapeutics* 2018 Oct 3;14(10):2382-90.
   Status: Published

List of abbreviations

AIDS: Acquired Immunodeficiency Syndrome

ART: Antiretroviral therapy

ARV: Antiretroviral drugs

BCG: Bacillus Calmette–Guérin

CI: Confidence intervals

CrIs: Credible intervals

DHS: Demographic and health survey

DIC: Deviance Information Criterion

DTP: Diphtheria-tetanus-pertussis

EPI: Expanded Programme on Immunization

GAPPD: Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea

GAVI: Global Alliance for Vaccines and Immunisation

GDP: Gross domestic product

GVAP: Global Vaccine Action Plan

HAART: Highly active antiretroviral therapy

HDI: Human Development Index

HIV: Human Immunodeficiency Virus

HI: HIV-infected

HU: HIV-uninfected

Hib: *Haemophilus influenzae* type B

HIV: Human immunodeficiency virus

ICC: Intra-cluster correlation

MOR: Median odds ratio

OR: Odds ratio

PCV: Pneumococcal conjugate vaccine

PCV9: 9-valent Pneumococcal conjugate vaccine

PCV13: 13-valent pneumococcal conjugate vaccine

PMTCT: Prevention of mother-to-child transmission.

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

PRV: Pentavalent rotavirus

RCT: Randomised controlled trials

RV: Rotavirus

UNICEF: United Nations Children's Fund

US$: United States Dollar

WHO: World Health Organization

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CHAPTER 1: General Introduction

Background

HIV epidemiology among children in sub-Saharan Africa

Human immunodeficiency virus (HIV) infection is a major health challenge and a leading cause of disability-adjusted life years/disease burden especially in the low- and middle-income countries.[1,2] The epidemic mainly affects sub-Saharan Africa with about 75% of the global burden of the disease.[3,4] HIV thrived in these countries due to the combination of factors such as inadequate access to healthcare, poor socio-economic conditions, political unrest leading to displacement, gender inequalities and harmful cultural practices, among others. [5]

Between 2001 and 2014, new HIV infections declined across all age groups with the most rapid reduction in children under-five years of age.[6] This decline was mainly due to the comprehensive implementation of prevention of mother-to-child transmission of HIV programmes and the provision of antiretroviral therapy (ART). Notwithstanding the progress made, many HIV-infected children still lack access to ART. Globally, about 1.8 million children aged under 15 years were living with HIV with 90% of these coming from sub-Saharan Africa and about 31% having access to ART in 2017 [4] (as shown in Figure 1). The incidence of new HIV infections among children also declined in 2017 but there were still 180,000 new infections that year alone.[4]

This recent progress is very different from the situation in the early 1980s when Kaposi's Sarcoma started emerging in younger patients as well as an aggressive form of pneumonia known as *Pneumocystis pneumonia*.[7] Additional opportunistic infections started evolving leading to the full-blown disease state of HIV known as Acquired Immune Deficiency Syndrome (AIDS). By the 1990s, AIDS became a leading cause of death in many countries. In 2010, The US Agency for International Development (USAID) estimated that 40 million African children had lost one or both parents to AIDS.[7]

Vaccination among HIV-infected and HIV-exposed children in sub-Saharan Africa

Vaccination has been demonstrated to be a cost-effective and beneficial public-health intervention to protect children, adolescents and adults from vaccine-preventable diseases. HIV-infected children are more susceptible to vaccine-preventable diseases such as tuberculosis, pneumonia, viral hepatitis etc. [8,9] Vaccination is essential in HIV-infected patients because of their increased risk of developing various infectious diseases due to their defective immune systems. It is therefore paramount to focus on the vaccination of HIV-infected patients in developing countries where many still have limited access to HIV diagnosis, treatment and care.[3] Studies from sub-Saharan Africa show that the coverage of routine vaccinations is low in some of these countries and inadequate to meet the Global Vaccine Action Plan (GVAP) targets.[10-12] Some African countries have low, stagnant or even decreasing immunisation coverage over the years. Only 26% of African countries had achieved ≥ 90% national coverage for vaccines included in their national immunisation schedule by World Health Organization (WHO) in 2014.[13] Africa accounts for about 34% of the global vaccine-preventable disease burden, and is also responsible for the highest proportion of under-five mortality from these diseases.[14]

Immunisation of children is one of the essential services that are vital for the attainment of Universal Health Coverage. However, lack of access and infrastructure is a big challenge in the provision of this service in sub-Saharan Africa. About 400 million people lack access to at least one of the six essential health services such as child immunisation or family planning services.[15,16] This lack of accessibility to service and infrastructures is responsible for significant inequalities across various subgroups among sub-Saharan African countries. Some African countries are also in a state of conflict including parts of Nigeria, South Sudan and the Democratic Republic of Congo with resultant disruption or collapse of essential primary healthcare services. In a conflict situation, the immunisation services are adversely affected. Although polio is no longer endemic in sub-Sahara Africa, many countries are still at risk of re-infection, particularly those in the 'poliovirus importation belt' which stretches from West Africa to the Horn of Africa.[17]

The World Health Organization Expanded Programme on Immunisation in conjunction with the United Nations Children's Fund recommends an accelerated immunisation schedule for both HIV-infected children and non-infected children (Table 1).[18] However, the childhood immunisation schedule may vary slightly among the countries. Adequate vaccination coverage is essential in

HIV-infected and HIV-exposed children because they are highly susceptible to more severe forms of some vaccine-preventable diseases with increased risk of mortality.[19,20]

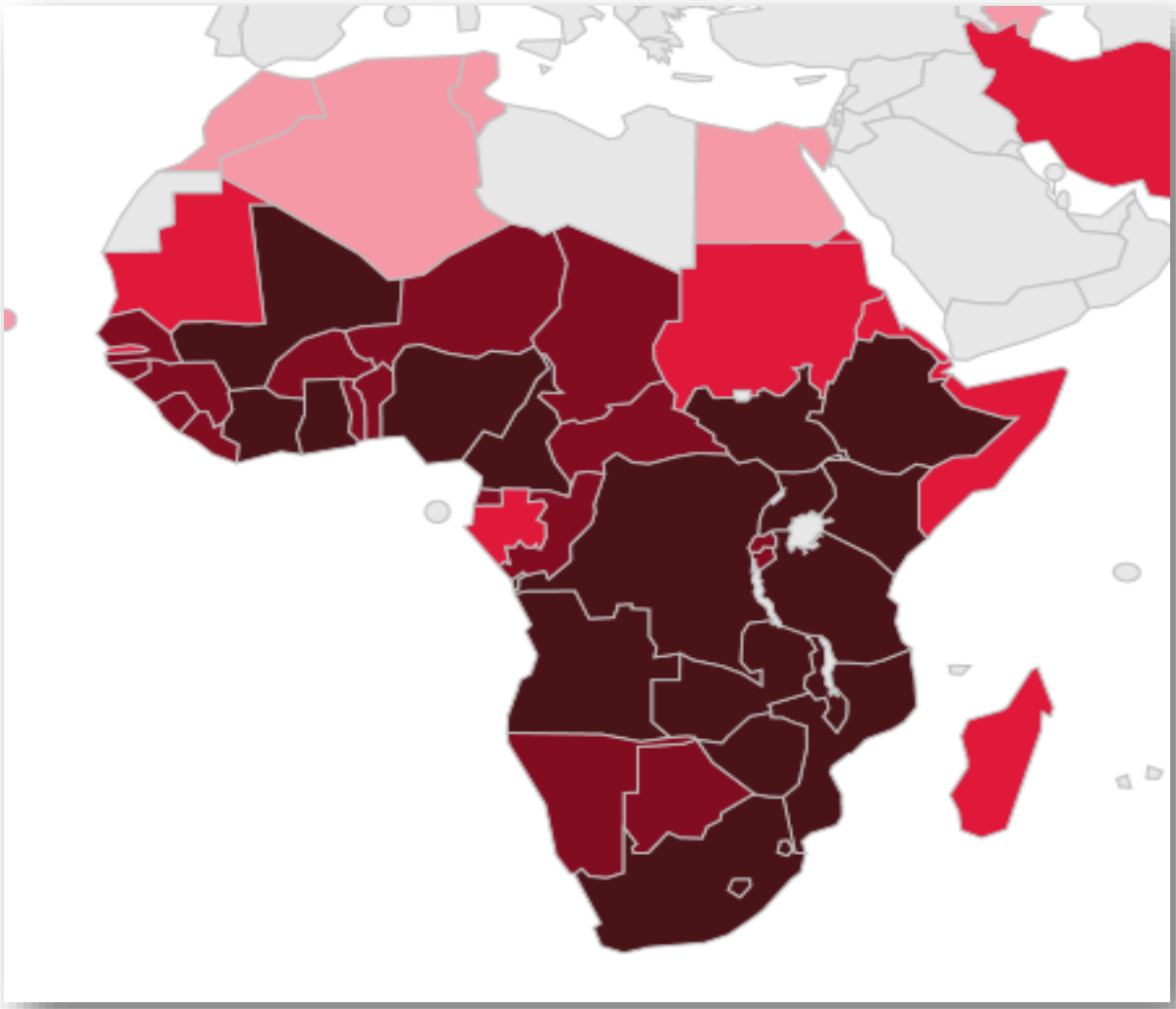

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Figure 1: A map showing the number of children aged 0-14 years old living with HIV in sub-Saharan Africa (2017) [4]

Vaccination of both HIV-infected and non-infected children played the critical role in achieving the Millennium Development Goal 4 targeted at reducing deaths in children under-five years of age.[17] In 2008, vaccine-preventable diseases were responsible for about 1.5 million deaths in children under-five years of age and this is estimated to be about 17% of all under-five deaths in that particular year.[21] Sustainable Development Goal 3.8 is also concerned with vaccination/immunisation strategies especially regarding the attainment of Universal Health Coverage via vaccines for all age groups.[22]

Table 1: Adapted summary of WHO position papers for recommended routine immunisations for children in most sub-Saharan African countries[18]

Antigens		Frequency of dosage
Bacillus Calmette–Guérin		One dose
Hepatitis B		3-4-doses
Oral polio/Inactivated polio		3-4 doses
Diphtheria, Tetanus and Pertussis		Three doses with two boosters at 12-23 months and 4-7 years
Haemophilus Influenzae type b	**Option 1**	Three doses
	Option 2	2 or 3 doses, with a booster at least six months after the last dose
Pneumococcal conjugate	**Option 1**	Three doses
	Option 2	Two doses before six months of age, plus booster dose at 9-15 months of age
Rotavirus		2 or 3 doses
Measles		Two doses
Rubella		One dose
Yellow Fever		One dose

Maternal HIV status and its association with childhood vaccination coverage

The association between maternal HIV status and childhood vaccination is of public health significance in countries with high HIV prevalence. Studies have shown that household wealth, maternal age, distance to healthcare facilities and maternal education are the main determinants of childhood vaccination in some African population.[23-25] However, HIV-exposed children have increased risk of mortality because HIV-infected mothers may not be predisposed to take the children for vaccination due to their generalised physical weakness as well as lack of transportation fees to access the services at the health centres.[26,27] The mothers may also avoid the healthcare clinics in their communities due to fear of stigma and discrimination.[28] There is uncertainty on maternal HIV status and its association to childhood vaccination coverage among HIV-exposed and infected children in Africa. Findings from both Ugandan and South Africa cohorts showed that children of HIV-infected mothers were less likely to be vaccinated for all routine vaccines than children born to non–infected mothers.[26,29] However, these findings cannot be generalised for the African population. HIV-exposed infants are those born to HIV-infected mothers and whose HIV status is not yet determined, while HIV-infected infants are the ones with confirmed HIV-infected status.

Study rationale

The vaccination rates of children remain insufficient for vaccine-preventable diseases in many African countries.[13] Low vaccination coverage translates to having numerous unvaccinated and under-vaccinated HIV-infected and HIV-exposed children who will eventually die from preventable diseases at a higher rate than their immunocompetent age counterparts.[19,20] Different care and treatment guidelines pinpoint vaccination as a crucial preventive strategy for HIV-infected patients [30,31] but data regarding the use of some of the vaccines among people living with HIV are still very scanty.[32] Experts using evidenced-based approaches on vaccination of immunocompromised individuals made specific recommendations for vaccination against major vaccine-preventable diseases for these patients but with limited proofs.[33] There have been few previous reviews on efficacy and effectiveness of pneumococcal and *Haemophilus influenza*e b vaccines against diseases in HIV-infected and exposed children but these studies were not systematic reviews and did not specify the disease outcomes.[34,35] The experts also identified

research gaps for future investigation. One of the gaps in knowledge was that of understanding the mediators of vaccine protection, adverse effects and basic aspects of the epidemiology of various vaccine-preventable diseases.[31] The changing pattern of some vaccine-preventable diseases is poorly understood, and this changing pattern and epidemiology makes it paramount to have a better understanding of these diseases because of possible resurgence and epidemics in the future.[33] The suboptimal uptake of vaccines in sub-Saharan Africa coupled with the high HIV burden is a risk factor that may facilitate future outbreaks. [33,36]

Ndirangu et al. [29] showed that there is a lesser likelihood of vaccination in children whose mothers are living with HIV and that this contributes significantly to the disparity in vaccination coverage between infants of HIV-infected and non-infected mothers. There is, however, limited information on whether the maternal HIV-infection status is associated with childhood immunisation coverage in general African populations.[29] Understanding the association between the mother's HIV status and the vaccination status of her HIV-exposed child is of great importance in sub-Saharan African countries with high HIV prevalence. [37] Valour et al. also showed that determinants for vaccine uptake among the HIV-infected population were mostly not evidence-based.[32] Exploring the effect of maternal HIV status on childhood vaccination among children in sub-Saharan Africa is critical to inform vaccine-preventable disease-prevention strategies and to develop interventions to improve vaccination coverage in HIV-infected and exposed children.

The identified gaps warrant the use of evidence-based research approaches to have a better understanding of vaccine-preventable diseases and coverage amongst HIV-infected children in sub-Saharan Africa. An evidence-based practice approach [38] will go a long way in improving the effectiveness, efficiency and sustainability of vaccination and immunisation policies targeted at HIV-infected and HIV-exposed children in sub-Saharan Africa. Evidence-based practice will also assist in developing appropriate remedial public-health interventions to address the observed challenges working against vaccination programmes among HIV-infected children including the Expanded Programme on Immunisation in some African countries.[39,40] Evidence-based research addresses the issue of information overload and helps decision-makers to filter growing quantities of published systematic reviews.[40] Further synthesis of all available evidence is required to provide reliable and easily accessible information to decision-makers, healthcare workers and the community of people living with HIV.

This research study focuses on the vaccines that are part of the Expanded Programme on Immunisation in African countries with high HIV prevalence. The study will concentrate on the following vaccine antigens: Hepatitis B; Bacillus Calmette–Guérin; diphtheria, tetanus and pertussis; *Haemophilus influenzae* type b; polio; pneumococcal conjugate; measles; rotavirus; rubella and yellow fever. The vaccine-preventable diseases of interest are as follows: tuberculosis, poliomyelitis, rotavirus gastroenteritis, diphtheria, tetanus, pertussis, pneumococcal diseases, measles, rubella and yellow fever.

Aim and objectives

Overall study goal

This research project set out general and specific objectives as described below:

The goal of this study is to determine:

- the burden of vaccine-preventable diseases;
- efficacy and effectiveness of vaccines;
- association between vaccination coverage and maternal HIV status and;
- differential morbidity benefit concerning HIV infection among sub-Saharan African children.

Specific objectives:

Workstream #1 (Evidence synthesis of existing studies)

1. To assess the burden of vaccine-preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan African countries.
2. To evaluate the efficacy and effectiveness of vaccines among HIV-infected and HIV-exposed children.

Workstream #2 (Secondary analyses of existing data sets)

1. To examine the vaccination coverage and the relationship between various country-level characteristics among sub-Saharan African children with respect to the maternal HIV status.
2. To develop and test models for non-uptake of vaccines among the children of HIV-infected mothers.

3. To determine the prevalence of symptoms of acute respiratory infections and episodes of diarrhoea; and the relationship of maternal HIV status with morbidity benefits of vaccine uptake among sub-Saharan African children.
4. To examine the role of the socio-economic factors in relation to uptake of DTP3 vaccines among HIV-exposed children.

Data sources

The study used various vaccines, vaccination, and HIV data from selected electronic databases, demographic and health surveys (DHS), WHO position papers, trial registers and experts. Articles and data were identified from 1980 to the date of commencement of each section of the doctoral research studies. DHS are nationally-representative household surveys conducted in low-and-middle-income countries.[41] The surveys provide data for a wide range of indicators in the areas of population, health, and nutrition.

This research used the three doses of diphtheria-tetanus-pertussis vaccines (DTP3) as a variable for vaccination status. DTP3 is a key indicator used by international and national organisations such as the United Nations Children's Fund (UNICEF) and WHO for assessing the effectiveness of childhood immunisation services.[36] The series of immunisations known as DTP can prevent diphtheria, pertussis (whooping cough) and tetanus, but these three diseases still kill 600,000 children and afflict millions of others every year in developing countries. The percentage of children receiving the final dose (DTP3) is therefore a revealing and vital gauge of how well countries are providing immunisation coverage for their children.[36] To be fully protected, DTP-containing vaccines are normally given in three doses at the age of 6, 10 and 14 weeks with three booster doses at 12-23 months, 4-7 years and 9-15 years. Diphtheria toxoid-containing vaccines are given to the older children as a booster vaccine.[18]

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CHAPTER 2: The burden of vaccine-preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa: a systematic review and meta-analysis

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Abstract

There are knowledge gaps regarding evidence-based research on the burden of vaccine-preventable diseases among human immunodeficiency virus (HIV)-infected and HIV-exposed children aged <18years in sub-Saharan Africa. It is therefore essential to determine the trend and current burden of vaccine-preventable disease epidemiology. We completed a systematic review of the literature and a meta-analysis to identify the incidence, prevalence and case-fatality rates (CFR) attributed to various vaccine-preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa. The trends in the prevalence of vaccine-preventable diseases among HIV-infected and HIV-exposed children were also determined. Nine studies on tuberculosis (TB) were pooled to give an overall incidence rate estimate of 60 (95% confidence interval [CI] 30 – 70) per 1,000 child-years. The incidence of pneumococcal infections varied between 109-1509 per 100,000 while pertussis was between 2.9 and3.7 per 1000 child-year. Twenty-two TB prevalence studies reported an estimated prevalence of 16%. Fifteen prevalence studies on hepatitis B infection were pooled together with an estimated prevalence of 5%. The pooled prevalence for pneumococcal infections was 2% while rotavirus diarrhoea reported a prevalence of 13%. Twenty-nine studies on TB were pooled to give an overall case-fatality rate estimate of 17% while pneumococcal infections in HIV-infected and exposed children were pooled together with a resultant rate of 15%. Some of the vaccine-preventable diseases still have high incidences, prevalence and CFR among HIV-infected and HIV-exposed children in sub-Saharan Africa. There is also a dearth of research data on the burden of several vaccine-preventable diseases among HIV-infected and exposed children and a need for more studies in this area.

***Keywords*:** HIV; vaccine-preventable diseases; sub-Saharan Africa; burden

Background

Human immunodeficiency virus (HIV) infection remains a leading public-health challenge and a principal cause of the infectious disease burden in low- and middle-income countries especially in sub-Saharan Africa.[1] This region accounts for the bulk of HIV infection with about 36.7 million people living with the disease an estimated 75% of the global burden.[2,3] It was also estimated that approximately 2.1 million children aged under 15 years were living with HIV with the majority coming from sub-Saharan Africa and about 31% having access to antiretroviral therapy in 2014.[4] The incidence of HIV infections among children declined in 2014 but there were still 220,000 new infections that year alone.[4] HIV-infected children have an increased risk of developing various vaccine-preventable diseases due to their defective immune systems.[5] This makes it crucial to focus on the vaccination of HIV-infected and exposed children. The majority of these children are also residents of low-and-middle-income countries characterised by limited access to HIV diagnosis, treatment and care.[2]

Vaccination against various vaccine-preventable diseases has been proven to be a beneficial and cost-effective public-health measure for protecting children, adolescents and adults from these diseases, thereby reducing the morbidity and mortality attributable to them.[6,7] Coverage of routine vaccinations is still low in some developing countries and not sufficient to meet the Global Vaccine Action Plan (GVAP) targets.[8–10] Some African countries have low or decreasing immunisation coverage over the years with some not achieving ≥ 90% national coverage for vaccines included in their national immunisation schedule by the World Health Organization (WHO) in 2016.[11] Sub-Saharan African countries account for about 34% of the global vaccine-preventable diseases burden, and are also responsible for the highest proportion of under-five mortality from these diseases.[12]

Recently, most developing countries have included routine childhood vaccines such as hepatitis B; Bacillus Calmette–Guérin (BCG); diphtheria, tetanus and pertussis (DTP); *Haemophilus influenzae* type b (Hib); polio; pneumococcal conjugate; measles; rotavirus (RV), rubella and yellow fever vaccines in their national Expanded Programme on Immunisation (EPI).[13] These vaccines also protect against diseases such as tuberculosis, poliomyelitis, rotavirus gastroenteritis, diphtheria, tetanus, pertussis, pneumococcal diseases, hepatitis B infection, rubella, measles and yellow fever.

The gap in knowledge, especially in terms of evidence-based research, on the burden of vaccine-preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa, warrants this study.[14] This study completed a systematic review of literature and meta-analysis to identify the incidence, prevalence and mortality due to various vaccine-preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa since the advent of HIV in the 1980s. This study is essential in determining the trend and current burden of vaccine-preventable disease epidemiology in sub-Saharan Africa.

Objectives

Primary objectives

1. To appraise all available published literature on the incidence and prevalence of vaccine-preventable diseases such as tuberculosis, poliomyelitis, hepatitis B virus infection, rotavirus gastroenteritis, diphtheria, tetanus, pertussis, pneumococcal diseases, measles, rubella and yellow fever among HIV-infected and HIV-exposed children in sub-Saharan Africa.
2. To determine the trend in the incidence and/or prevalence of vaccine-preventable diseases such as tuberculosis, poliomyelitis, hepatitis B virus infection, rotavirus gastroenteritis, diphtheria, tetanus, pertussis, pneumococcal diseases, measles, rubella and yellow fever among HIV-infected and HIV-exposed children in sub-Saharan Africa from 1980 to 2018.

Secondary objective

1. To describe the case-fatality rate ascribed to vaccine-preventable diseases such as tuberculosis, poliomyelitis, hepatitis B virus infection, rotavirus gastroenteritis, diphtheria, tetanus, pertussis, pneumococcal diseases, measles, rubella and yellow fever among HIV-infected and HIV-exposed children in sub-Saharan Africa.

Methods and design

This systematic review was developed in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2015 statement.[15] The review was registered with PROSPERO (International prospective register of systematic reviews) (CRD42018095341).

Inclusion criteria

Type of participants: The review included sub-Saharan African children who are HIV-infected or HIV-exposed and aged <18 years old.

Types of outcome:

We included studies that reported the incidence, prevalence and case-fatality rates (CFR) as outcomes in HIV-infected and HIV-exposed children.

Primary outcomes

Prevalence was defined as proportions of all individuals suspected of having specific vaccine-preventable diseases with confirmed laboratory diagnosis or proportions of individuals fulfilling clinical case definition for specific vaccine-preventable diseases. Incidence was defined as the number of new cases of different vaccine-preventable diseases that occur during a given period in the defined population.

We also determined the trend in the incidence and/or prevalence of vaccine-preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa from 1980 to 2018.

Secondary outcomes

We included CFRs associated with vaccine-preventable diseases. Case fatality was described as mortality among confirmed or probable cases for a specific vaccine-preventable disease.

Type of studies: The review included cohort studies, case-control studies, cross-sectional studies and other observational studies. We planned to include studies that involved any of the following vaccine-preventable diseases:

i. Tuberculosis (TB)
ii. Poliomyelitis
iii. Hepatitis B virus infection (HBV)
iv. Rotavirus gastroenteritis
v. Diphtheria
vi. Tetanus
vii. Pertussis
viii. Pneumococcal diseases
ix. Measles
x. Rubella

xi. Yellow fever

Exclusion criteria

- Intervention studies
- Unclear diagnostic criteria

Search strategy methods for the identification of studies

A comprehensive search strategy was developed to identify relevant studies up to August 2018, regardless of publication status or language. Scopus, Web of Science, MEDLINE via PubMed and CINAHL were searched for relevant publications. The search process was complemented by reviewing citations of all identified eligible studies. We also searched relevant World Health Organization position papers and documents on vaccines. (See Appendix for PubMed search strategy).

Selection of eligible studies

Two of the authors, (OOA and AA) screened the search results using the abstract titles. They also independently went through the full text of potential studies to assess whether they met the required inclusion criteria. Non-human studies, reviews, intervention studies, letters, commentaries and editorials were excluded. Studies not written in English, French, German, Spanish, Portuguese or Dutch were excluded. We resolved disagreements by consensus.

Data collection process

The two authors then extracted data from text, tables and figures. The data were recorded on a standardised form. We planned to contact authors of included studies in case of unclear or missing data.

The following data were extracted from selected studies:

- Study characteristics including period and design.
- Vaccine-preventable diseases patient characteristics such as age and HIV status.
- Prevalence or incidence of vaccine-preventable diseases: confirmed cases and cases meeting the clinical definition.
- Diagnostic methods: laboratory methods and clinical case definitions.
- Death attributed to vaccine-preventable diseases.

Risk of bias in individual studies

The risk of bias and quality of the included studies were assessed with the Newcastle-Ottawa Quality Scale.[16] The criteria assessed included the following (1) selection of participants, (2) comparability, (3) exposure, and (4) outcome.

Data synthesis

OOA summarised the incidence and prevalence of various vaccine-preventable diseases. Where possible, incidence and prevalence data from each of the included studies were combined by random effects meta-analysis in accordance with the Mantel-Haenszel method.

Heterogeneity was evaluated using the Chi-squared test of homogeneity (significant for $P < 0.1$) and quantified using the I-squared statistic (>50% substantial heterogeneity).[17] Subgroup analyses were conducted in cases with substantial heterogeneity. Subgroup analysis was conducted using the following variables: period of study (1991- 2000, 2001-2010 and 2011 – 2018). We also used funnel plot regression to assess publication bias. STATA software version 14.0 (STATA Corporation, College Station, TX, USA) was used to do all calculations, the meta-analysis and generate forest plots.[18]

Additional analyses: Trend analysis

We examined time trends in the incidence and prevalence of vaccine-preventable diseases estimates using Poisson regression models with the prevalence estimates as the outcome variable and the calendar year of the publication as the predictor. This method allows for estimation of time trends across individual calendar years to obtain average annual percentage change (AAPC), assuming that the rate of change is at a constant rate of the previous year. [19] The Poisson regression procedure fits a model of the following form:

$$\log\left(prevalence_y\right) = b_0 + b_1 y + \log(sample\,size) \qquad (1)$$

where *'cases'* equal prevalence estimates reported per year, log is the natural log, *b0* is the intercept, *b1* is the trend, *y* is the year – given as 0, 1, 2, … 18 (year 0 is 1970, year 1 is 1971, and so on to 2014), and log of 'sample size' was entered as the offset. The AAPC was calculated using the following formula:

$$AAPC = \left(e^{b_1} - 1\right) \times 100 \quad (2)$$

Results

Literature search and result

Figure 1 shows the study selection process reported in line with PRISMA guidelines. We identified 3430 publications through the search of different databases. We also identified 13 additional articles through the screening of reference lists of various related articles. We screened 188 full-text articles and selected 76 articles for inclusion in the review and 70 articles were suitable for the meta-analysis (Figure 1).

Study characteristics

Table 1 provides a summary of the included studies and the vaccine-preventable diseases of interest. The table shows that 45 articles reported on tuberculosis, 14 on hepatitis B virus infection, ten studies focused on pneumococcal infections, two on rotavirus gastroenteritis, three on measles and three on pertussis. The included articles consist of 41 cross-sectional studies, 31 cohort studies, four case-control studies and one time-series analysis.

South Africa had the highest number of published articles with 35 articles, Nigeria produced 10 articles, four were from Kenya, four from Ethiopia and two studies were conducted in multiple countries. The other studies were conducted in Rwanda, Tanzania, Cote d' Ivoire, Uganda, Malawi, Botswana, Zimbabwe, Zambia, Mozambique and Swaziland (Table 1). A total of 46,882 children were included in this review. HIV-infected children were included in 71 studies while two studies had both HIV-infected and HIV-exposed uninfected children, and one study with only HIV-exposed children. The included studies were conducted between 1992 and 2016.

Using the Newcastle-Ottawa Quality Scale for the quality assessment of the eligible studies, 11 articles scored eight points; 15 articles scored seven points; 27 articles scored six points; 15 articles scored five points; seven articles scored four points and two articles scored three points. The characteristics of the eligible studies are summarised in Table 1.

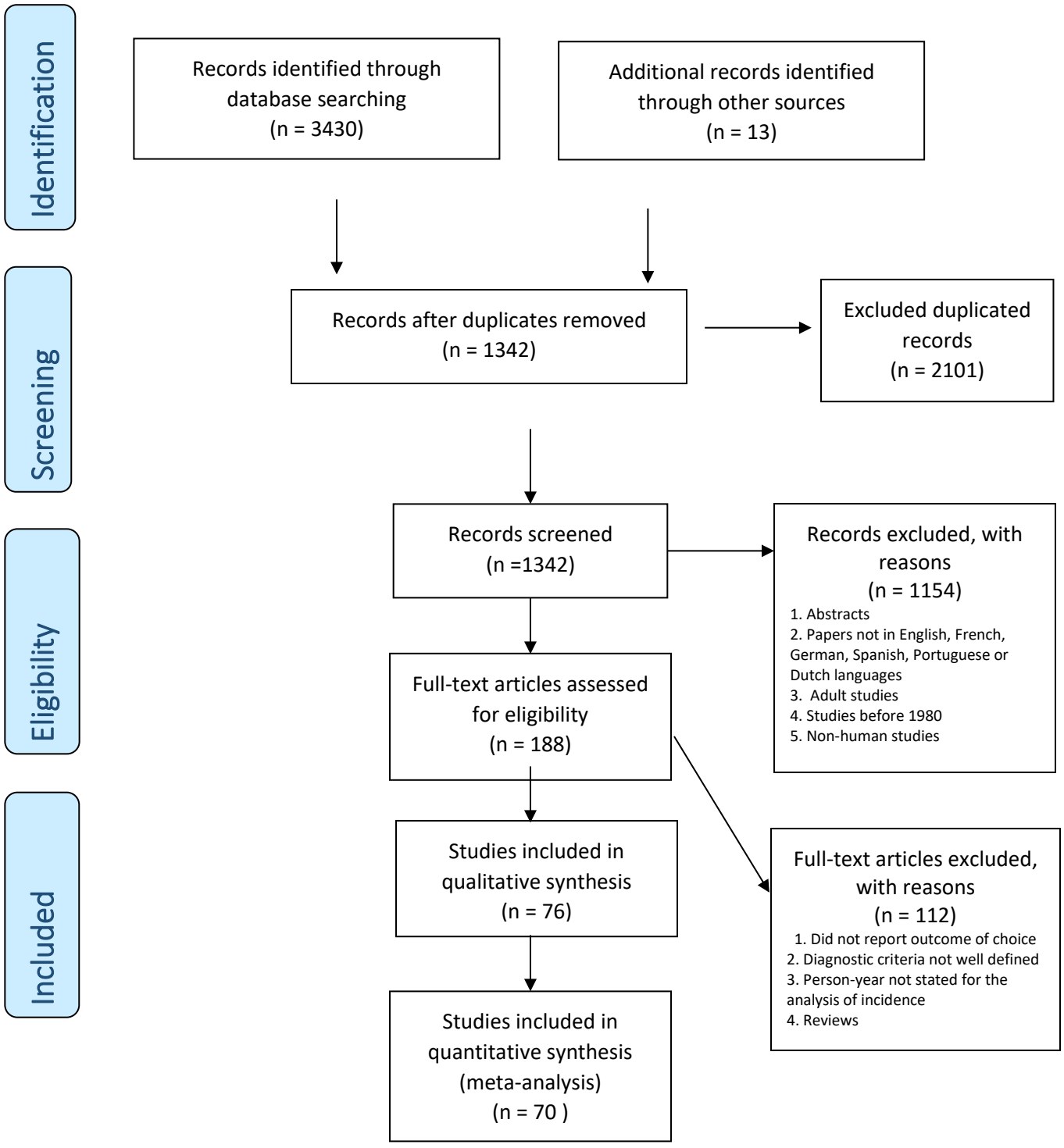

Figure 1: Flow diagram of the selection process

Table 1: Characteristics of the study population

First author and year	Study period	Study design	Country	Sample size	VPD	Outcomes	HIV status	Quality scores
Abuogi 2013[20]	2009 - 2010	Cohort	Kenya	689	Tuberculosis	C, I, P	HI	7
Adams 2014[21]	2006 - 2012	Cross-sectional	Tanzania	1193	Tuberculosis	C, P	HI	4
Alemu 2016[22]	2009 - 2014	Cohort	Ethiopia	645	Tuberculosis	I	HI	6
Anigilaje 2016[23]	2010 - 2013	Cohort	Nigeria	368	Tuberculosis	P	HI	8
Auld 2014[24]	2004 - 2008	Cohort	Cote d' Ivoire	2110	Tuberculosis	I, P	HI	8
Bakeera 2011[25]	2003 - 2006	Cohort	Uganda	1806	Tuberculosis	I, C	HI	8
Bonnet 2018[26]	2012 - 2014	Cohort	Uganda	113	Tuberculosis	C	HI	7
Braitstein 2009[27]	2001 - 2007	Cohort	Kenya	6,535	Tuberculosis	I, P	HI	8
Buck 2013[28]	2010	Cohort	Malawi	4874	Tuberculosis	C, P	HI	8
Carlucci 2017[29]	2012 - 2014	Cohort	Multiple	386	Tuberculosis	C	HI	8
Cavanaugh 2012[30]	2006 - 2007	Cross-sectional	Kenya	323	Tuberculosis	C	HI	6
Chaya 2016[31]	2006 - 2011	Cross-sectional	South Africa	47	Tuberculosis	I	HI	6
Cruz 2015[32]	NR	Cohort	Botswana	100	Tuberculosis	P	HI	6
Dangor 2013[33]	2005 - 2009	Time-series analysis	South Africa	1985	Tuberculosis	I	HI	7
De Maayar 2011[34]	NR	Cross-sectional	South Africa	58	Tuberculosis	P	HI	7
Ebonyi 2016[35]	2005 - 2013	Cohort	Nigeria	260	Tuberculosis	C	HI	8
Ebonyi 2016b[36]	2005-2012	Cohort	Nigeria	876	Tuberculosis	P	HI	8
Elenga 2005[37]	2000-2003	Cohort	Cote d' Ivoire	282	Tuberculosis	I	HI	8
Ferrand 2010[38]	2007-2008	Cross-sectional	Zimbabwe	139	Tuberculosis	P	HI	7
Hall 2017[39]	2005-2008	Cohort	South Africa	224	Tuberculosis	C	HI	8
Hesseling 2009a[40]	2004-2006	Cross-sectional	South Africa	3321	Tuberculosis	C	HI	6
Hesseling 2005[41]	1992-2000	Cohort	South Africa	93	Tuberculosis	C	HI	8
Hesseling 2006[42]	2002-2005	Cohort	South Africa	108	Tuberculosis	C, P	HI	7
Hesseling 2009b[43]	2004-2006	Cross-sectional	South Africa	3321	Tuberculosis	I, P	HI	7
Hicks 2014[44]	2009-2010	Cohort	South Africa	64	Tuberculosis	C	HI	6
Jeena 2000[45]	1995-1998	Cross-sectional	South Africa	27	Tuberculosis	P	HI	5
Kasambira 2011[46]	2006-2009	Cross-sectional	South Africa	270	Tuberculosis	P	HI	6
Madhi 2000b[47]	1996-1997	Cross-sectional	South Africa	67	Tuberculosis	C	HI	5
Meyers 2000[48]	1996	Cross-sectional	South Africa	144	Tuberculosis	P	HI	5

Mwangwa 2017[49]	2012-2013	Cohort	Multiple	17	Tuberculosis	C	HI	7
Obiagwu 2013[50]	2010	Cross-sectional	Nigeria	22	Tuberculosis, Measles	P	HI	6
Okechukwu 2011[51]	2007-2008	Cross-sectional	Nigeria	210	Tuberculosis	C, P	HI	6
Osman 2017[52]	2005-2012	Cohort	South Africa	3143	Tuberculosis	C	HI	6
Padayatchi 2006[53]	1993-2002	Cross-sectional	South Africa	6	Tuberculosis	C	HI	5
Palme 2002[54]	1995-1997	Cohort	Ethiopia	58	Tuberculosis	C	HI	6
Patel 2013[55]	2007-2009	Cohort	Congo DRC	31	Tuberculosis	C	HI	7
Robinson 2007[56]	1999-2001	Case-control	South Africa	47	Tuberculosis	P	HI	6
Rose 2012[57]	2008-2010	Cohort	Tanzania	54	Tuberculosis	P	HI	6
Schaaf 2007[58]	2003-2005	Cross-sectional	South Africa	133	Tuberculosis	C	HI	5
Soeters 2005[59]	2000-2001	Cross-sectional	South Africa	43	Tuberculosis	C	HI	4
Walters 2014[60]	2003-2010	Cohort	South Africa	494	Tuberculosis	C	HI	6
Walters 2008[61]	2003-2005	Cross-sectional	South Africa	137	Tuberculosis	C	HI	6
Westerlund 2014[62]	2003-2008	Cohort	Ethiopia	138	Tuberculosis	P	HI	7
Wiseman 2011[63]	2004-2006	Cross-sectional	South Africa	52	Tuberculosis	C	HI	5
Yotebieng 2010[64]	2004-2008	Cohort	South Africa	573	Tuberculosis	C	HI	6
Kouakoussui 2004[65]	2003	Cohort	Cote d'Ivoire	270	Tuberculosis	I	HI	7
Abera 2014[66]	2014	Cross-sectional	Ethiopia	253	HBV infection	P	HI	6
Ashir 2009[67]	2007	Case-control	Nigeria	284	HBV infection	P	HI	5
Beghin 2017[68]	2014	Cross-sectional	South Africa	183	HBV infection	P	HI	6
Chotun 2015[69]	2011 - 2012	Cross-sectional	South Africa	1000	HBV infection	P	HE	6
Uleanya 2016[70]	NR	Cross-sectional	Nigeria	140	HBV infection	P	HI	4
Dziuban 2013[71]	2009 - 2011	Cross-sectional	Swaziland	500	HBV infection	P	HI	3
Ikpeme 2013[72]	2010-2011	Cross-sectional	Nigeria	166	HBV infection	P	HI	4
Jooste 2016[73]	2015-2016	Cohort	South Africa	625	HBV infection	P	HI	7
Muro 2013[74]	2006-2008	Cross-sectional	Tanzania	157	HBV infection	P	HI	5
Mutwa 2013[75]	2010	Cohort	Rwanda	88	HBV infection	P	HI	7
Nwolisa 2013[76]	2010	Cross-sectional	Nigeria	139	HBV infection	P	HI	4
Sadoh 2011[77]	NR	Cross-sectional	Nigeria	155	HBV infection	P	HI	5
Telatela 2007[78]	2006	Cross-sectional	Tanzania	167	HBV infection	P	HI	4
Varo 2016[79]	2008-2010	Cross-sectional	Malawi	91	HBV infection	P	HI	3
Moss 2002[80]	1998-2000	Cross-sectional	Zambia	93	Measles	P	HI	6
Wirth 2015[81]	2009-2010	Case-control	Botswana	189	Measles	C	HI	5
du Plessis 2018[14]	2013 - 2015	Cross-sectional	South Africa	300	Pertussis	P	HI	6

Gill 2016[82]	2015	Cohort	Zambia	347	Pertussis	I	HI	7
Soofie 2016[83]	2015	Cross-sectional	South Africa	599	Pertussis	C, I, P	HE	5
Johnson 2000[84]	1996-1997	Cross-sectional	South Africa	31	Rotavirus gastroenteritis	P	HI	6
Moyo 2014[85]	2010-2011	Case-control	Tanzania	26	Rotavirus gastroenteritis	P	HI	5
Asbjörnsdóttir 2013[86]	1999-2002	Cohort	Kenya	388	Pneumococcal infection	C,I	HI	6
Nathoo 1996[87]	1993-1994	Cohort	Zimbabwe	168	Pneumococcal infection	P	HI	7
Zar 2001[88]	1998	Cross-sectional	South Africa	151	Pneumococcal infection	P	HI	6
Jones 1998[89]	1996	Cross-sectional	South Africa	25	Pneumococcal infection	C	HI	5
Roca 2010[90]	2004-2006	Cross-sectional	Mozambique	54	Pneumococcal infection	C	HI	6
Cohen 2016[91]	2009 - 2013	Cross-sectional	South Africa	211	Pneumococcal infection	I	HEU,HI	4
Nunes 2011[92]	2003-2008	Cross-sectional	South Africa	938	Pneumococcal infection	I	HI	6
von Mollendorf 2017a[93]	2009–2013	Cross-sectional	South Africa	495	Pneumococcal infection	C, I	HI	5
von Gottberg 2013[94]	2003-2008	Cross-sectional	South Africa	1749	Pneumococcal infection	I	HI	5
Nyasulu 2011[95]	2003-2005	Cross-sectional	South Africa	1124	Pneumococcal infection	C	HI	6

NR- Not recorded; C- Case-fatality rate; I – Incidence; P – Prevalence; Hib- Haemophilus influenzae type b; HI- HIV-infected; HE- HIV-exposed; HEU – HIV-exposed uninfected; VPD - vaccine–preventable diseases.

Incidence rates

Tuberculosis: Nine studies[20,22-25,27,37,40] on TB were pooled to give an overall incidence rate estimate of 60 (95% CI 30 – 70) per 1,000 child-years at risk for tuberculosis based on a random-effects model (I^2 = 99%; Figure 2). Subgroup analysis established change over time in incidence rates when comparing studies conducted before and after 2011. The pooled incidence rates for tuberculosis in those conducted before 2010 was 70 (95% CI -20 - 160) per 1,000 child-years[37,40] and 40 (95% CI 20 - 50) per 1,000 child-years in studies conducted between 2011 and 2018.[20,22-25,27] The heterogeneity of the TB incidence could not be explained by the subgroup analysis. Kouakoussui et al. reported TB incidence of 0.71 per 100 child/months before initiation of highly active antiretroviral therapy (HAART) and 0.16 per 100 child/months during HAART treatment among Ivorian HIV-infected children.[65]

Pneumococcal infections: Incidence of invasive pneumococcal disease among HIV-infected children aged <1 and 1–4 years was 1022 (95% CI 923–1123) per 100,000 and 198 (95% CI 178–220) per 100,000 respectively in 2008.[94] The incidence of pneumococcus-associated lower respiratory tract infection among HIV-exposed uninfected children was 109 (95% CI 47–214) per 100,000 and 629 (95% CI 130–1838) per 100,000 among HIV-infected children.[91] Ásbjörnsdóttir et al. reported the incidence of pneumonia among Kenyan HIV-exposed uninfected infants to be 900 (95% CI 800–1000) per 1,000 child-years.[86] Nunes et al. reported the incidence of invasive pneumococcal disease to be 1509 (95% CI 1350 – 1680) per 100,000 during early (HAART) and 742 (95% CI 644 – 851) during established-HAART eras for less than 18-year old South Africans.[92]

Pertussis: The incidence of pertussis among Zambian HIV-exposed infants was reported to be 3.7 (95% CI 0.9–10.1) per 1000 person-months [82] while Soofie et al. reported the incidence to be 2.9 (95% CI 1.8 – 4.5) per 1,000 child-years. [83]

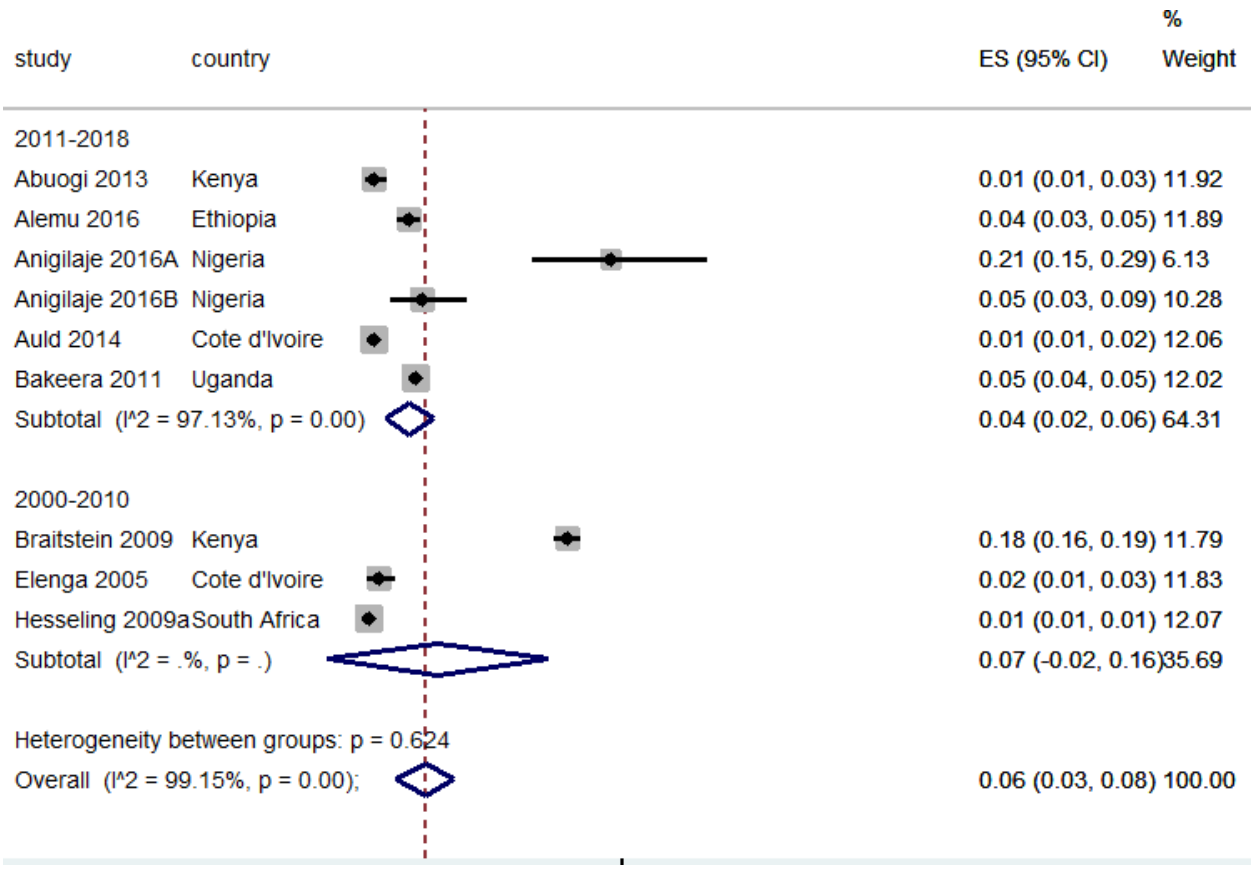

Figure 2: Forest plot of studies with data on incidence rates of tuberculosis in HIV-exposed children

Prevalence

Twenty-one TB prevalence studies were pooled together and reported estimated prevalence of 16% (95% CI 12 - 19, I^2 = 99%). For studies conducted within the period 1991-2000, the prevalence was 13% (95% CI 8 - 18)[45,48]; lower in 2001-2010 with an estimate of 8% (95% CI 5 - 11, I^2 = 96%)[27,38,42,43,56] and recorded the highest prevalence in recent years with 15% (95% CI 8 - 22, I^2 = 99)[20,21,23,24,26,28,32,34,36,46,50,51,57,62] (Figure 3). Fourteen prevalence studies on hepatitis B (HBV) infection in HIV-infected children were pooled together with an estimate prevalence of 5% (95% CI 4 - 7, I^2 = 90%). Studies conducted between 2001 and 2010 had a prevalence of 3% (95% CI 2 - 5) [67,68] and 4% (95% CI 3 – 6) between 2011 and 2018 [66,68,69,70-77,79] (Figure 4).

The pooled prevalence for pneumococcal infections was 2% (95% CI 1 – 4). There has been a reduction in prevalence from 9% (95% CI 5 - 14)[88] in 1996 to 1% (95% CI 0 – 5)[89] in 2001. Pooled

prevalence for pertussis was 3% (95% CI 2 - 4)[14,83] while measles was 6% (95% CI 2 – 10).[80,81] Two rotavirus diarrhoea prevalence studies were pooled together and reported an estimated prevalence of 13% (95% CI 8 - 17, I^2 = 0%).[84,85]

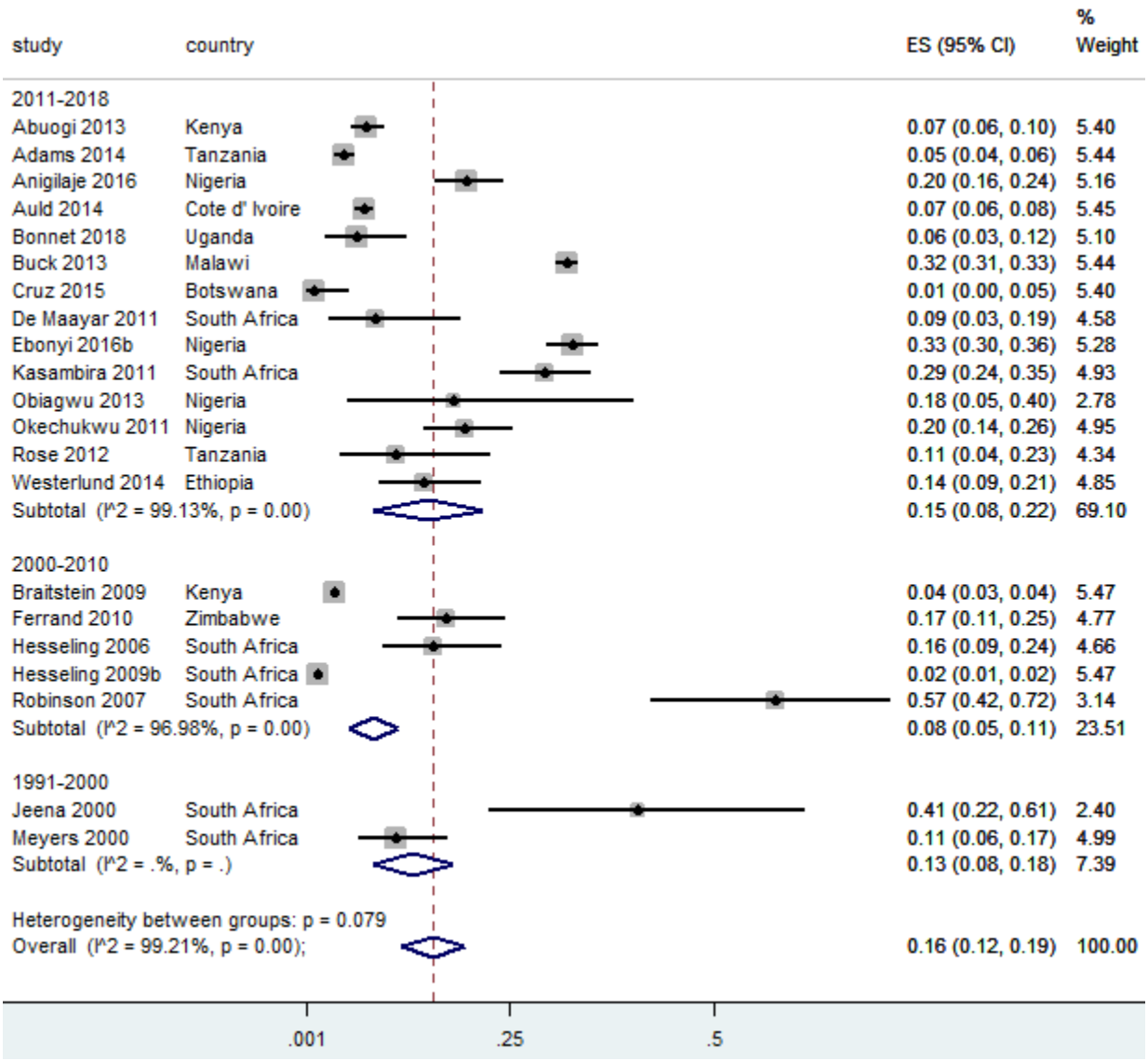

Figure 3: Forest plot of studies with data on the prevalence of tuberculosis in HIV-infected children

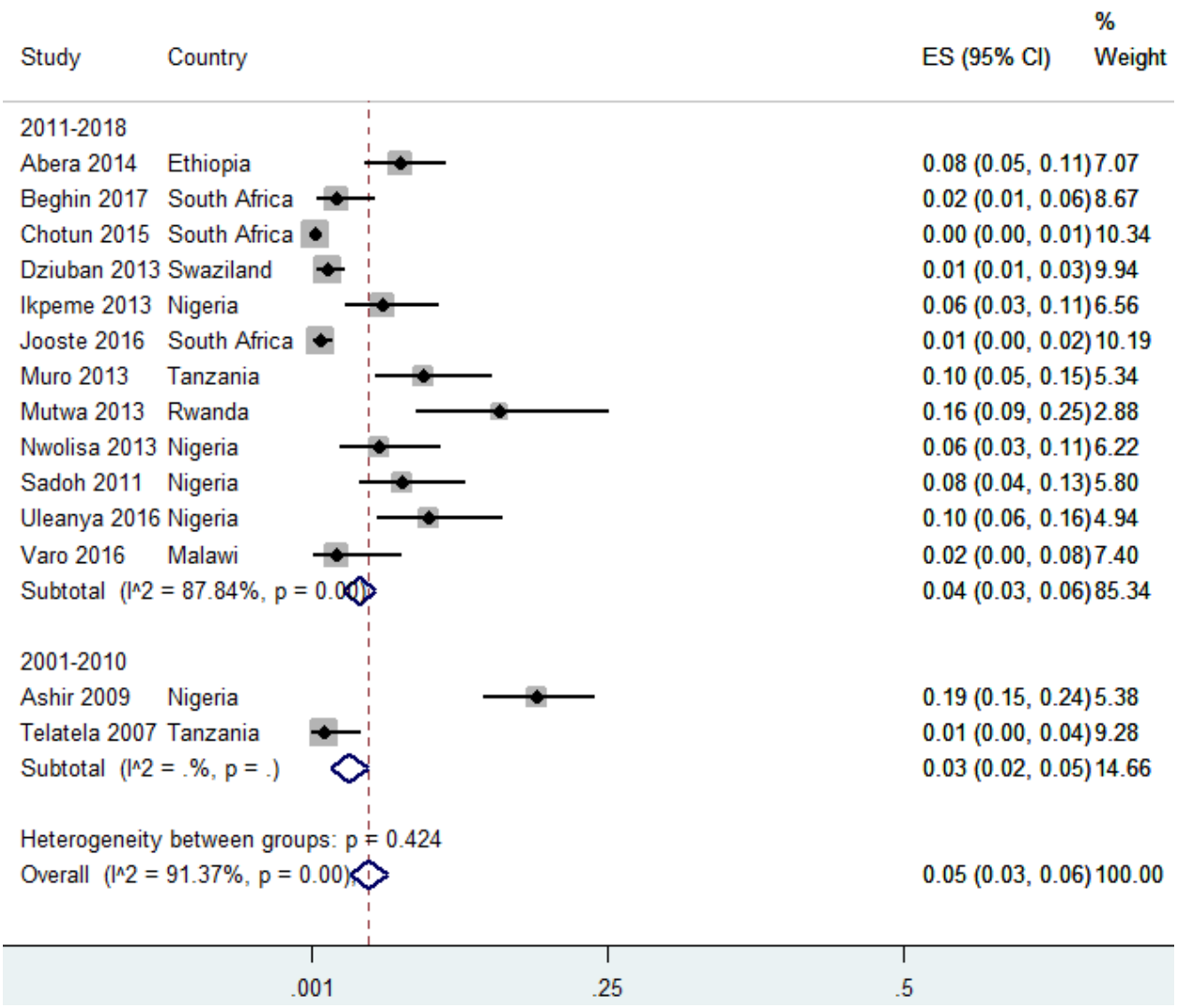

Figure 4: Forest plot of studies with data on the prevalence of hepatitis B virus infection in HIV-infected and HIV-exposed children

Trend in incidence and prevalence

We analysed the trend in TB incidence with respect to publication years. The trend was non-linear with a downtrend from 2000 to 2010 (at -12.5% per year) and a reduced downward trend from 2011 to 2018 (at -1.5 per year) as shown in Figure 5. The trend in HBV prevalence was also analysed. The trend was not linear, There was evidence of a downtrend from 2000 to 2010 (at -4.7% per year) and (at -5.3% per year) from 2011 to 2018 as shown in Figure 6. The TB prevalence

trend was also non-linear. There was evidence of initial downtrend from 2000 to 2010 (at -3.2% per year) and upward trend from 2011 to 2018 (at +32.7 per year).

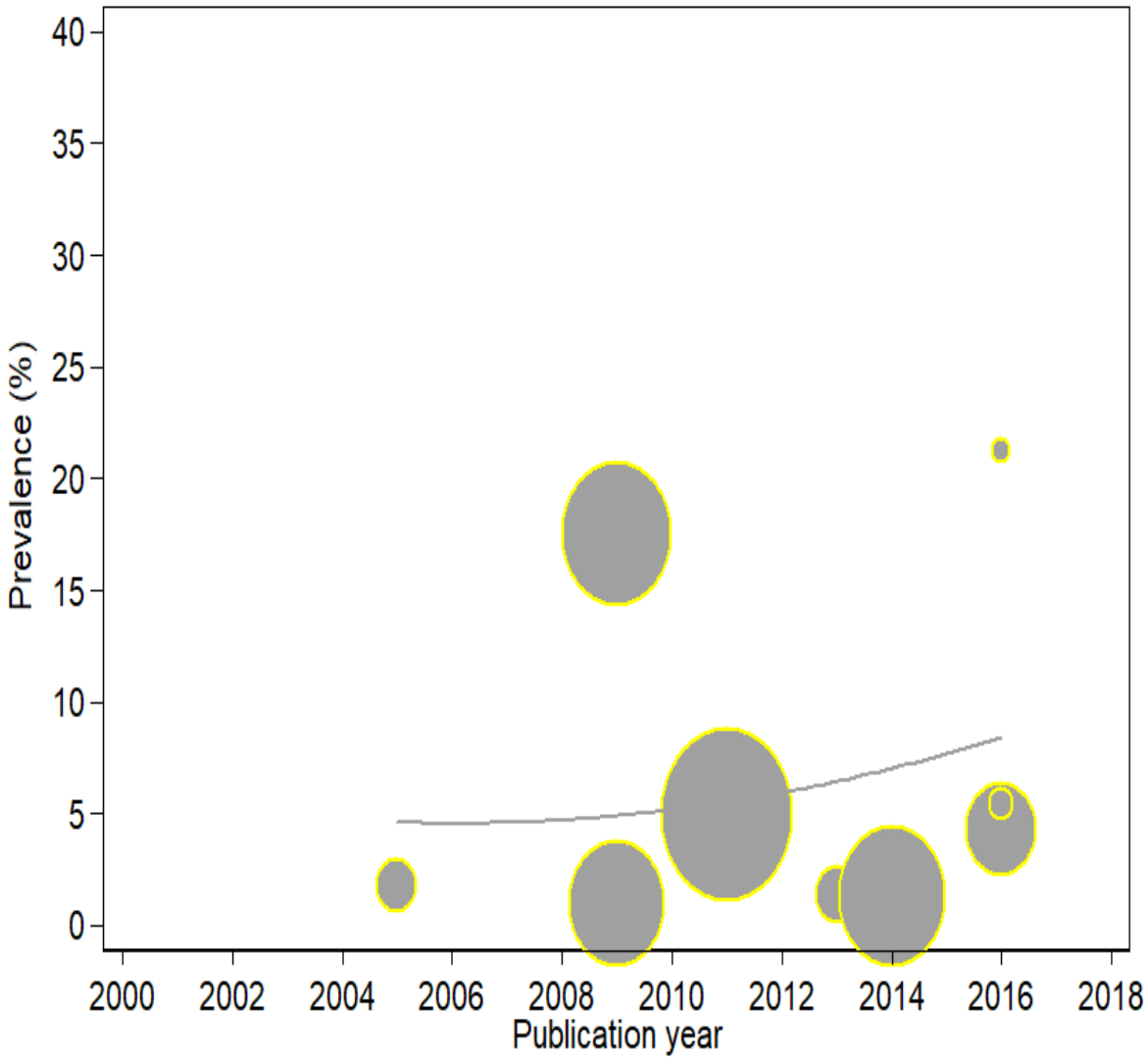

Figure 5: Trends in the incidence of tuberculosis in HIV-infected and exposed children with respect to publication years

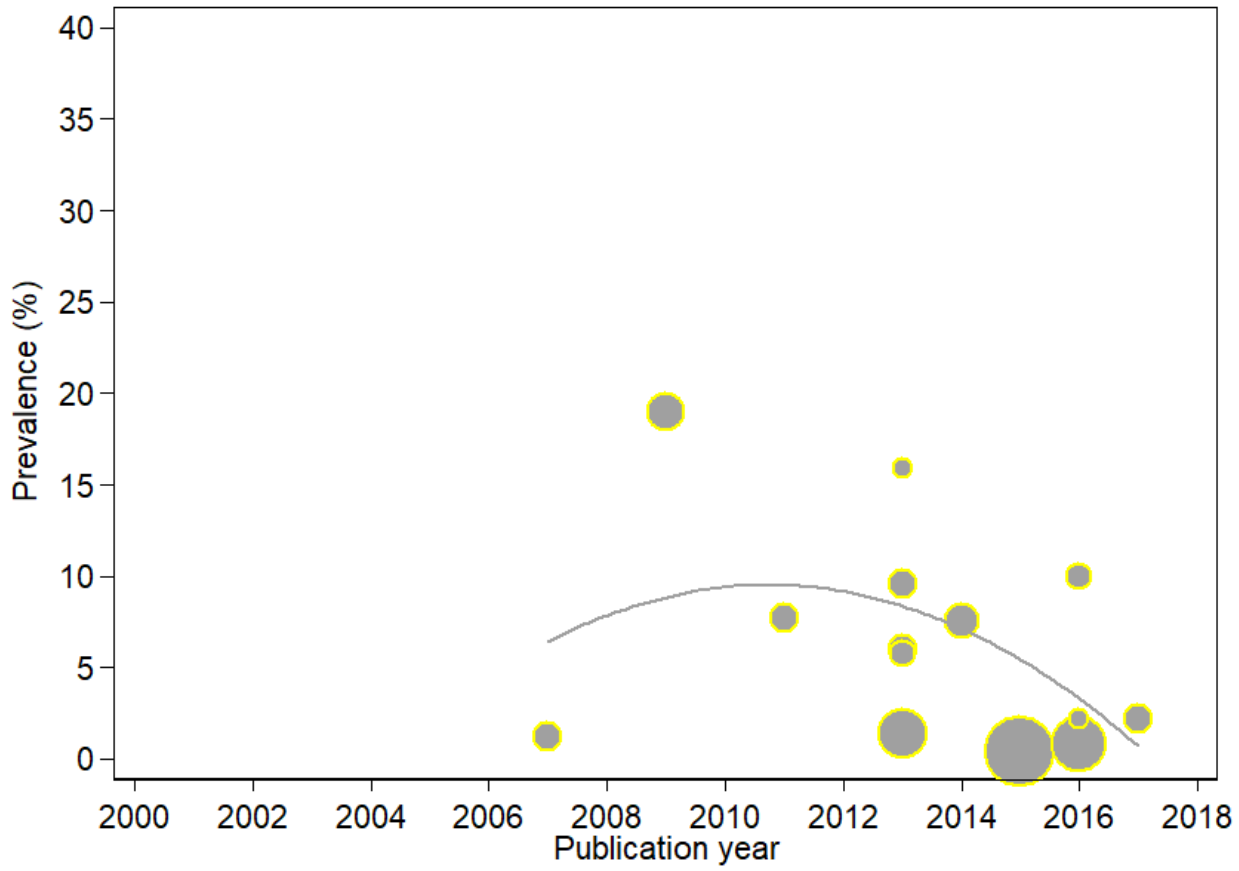

Figure 6: Trends in the prevalence of hepatitis B virus infection in HIV-infected and exposed children with respect to publication years

Case-fatality rates

Twenty-nine studies on TB were pooled to give an overall CFR estimate of 17% (95% CI: 13 - 20, I^2 = 95%) which translates to 17% of all TB cases dying from the disease. Subgroup analysis shows the CFR was 18% (95% CI 6 – 24)[47] in the 1991-2000 period, 6% (17 – 38, I^2 = 95%)[38,40-42,53,54,58,59,61,64] in 2001-2010 and 13% (95% CI 9 – 17, I^2 = 96%)[20,21,23,25,28-30,35,39,44,49,51,52,55,60,61] in 2011 – 2018. Four studies were pooled for pneumococcal infections CFRs in HIV-infected and exposed children with a resultant rate of 15% (95% CI 4 – 26, I^2 = 95%).[86,89,90,95] One study shows that pertussis has CFRs of 13% (95% CI 2 – 38) [83] and for measles the CFR was 1% (95% CI 0 - 4).[81]

Publication bias assessment

Funnel-plot analyses of studies reporting on the prevalence of TB revealed nil significant publication bias, with the P value for the Begg's test being 0.185 while the studies assessing the prevalence of HBV infection showed significant Begg's test with P value of 0.001 (Figure 7 and 8). Likewise, studies assessing the CFR of TB demonstrated no significant publication bias Begg's test P = 0.385 (Figure 9).

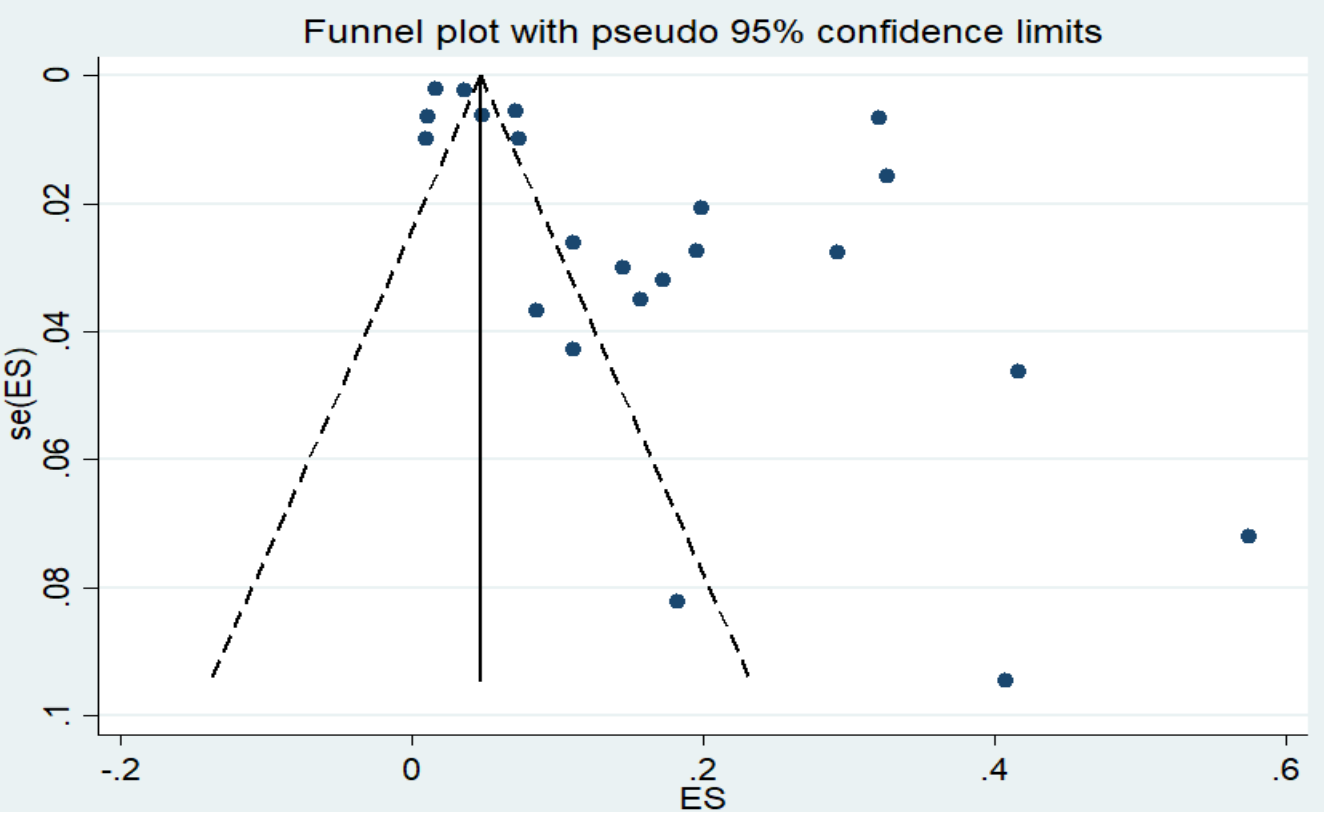

Figure 7: Funnel plot of studies reporting on the prevalence of tuberculosis in HIV-infected children

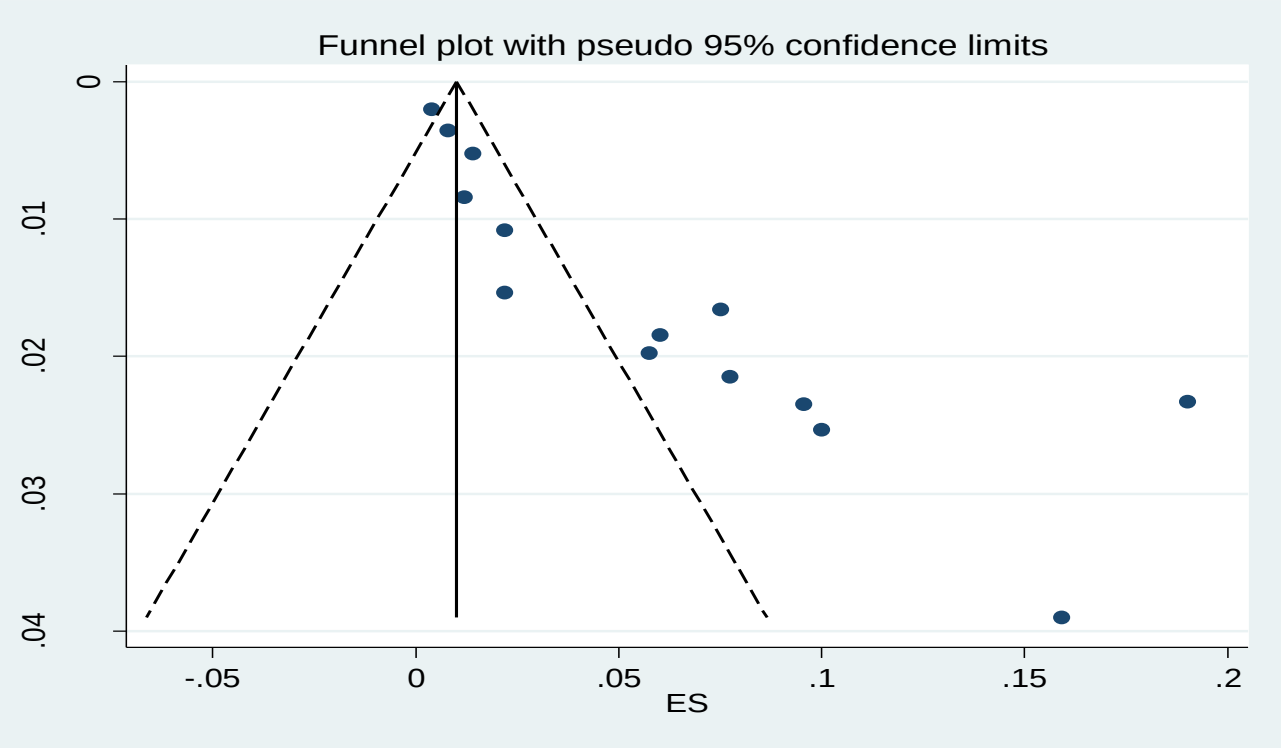

Figure 8: Funnel plot of studies reporting on the prevalence of hepatitis B virus infection in HIV-infected children

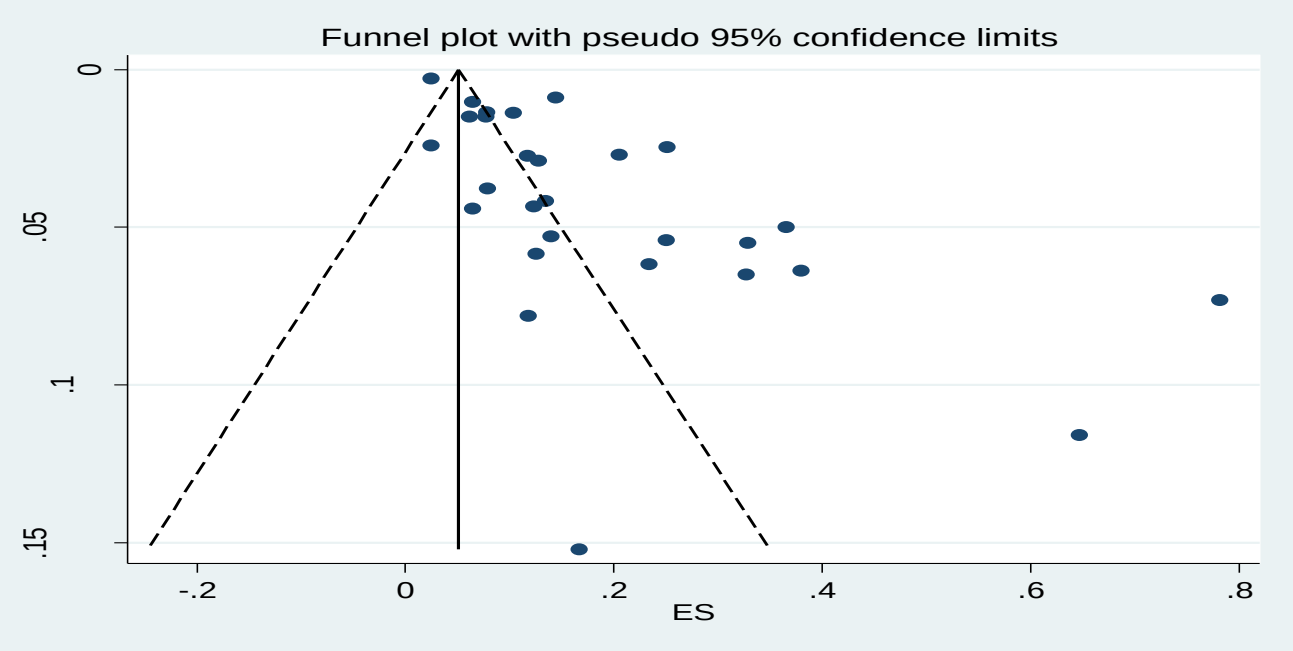

Figure 9: Funnel plot of studies reporting on the case-fatality rate of tuberculosis in HIV-infected children

Discussion

This study provides a comprehensive overview of the incidence rate, prevalence and case fatality rates of different vaccine-preventable diseases in HIV-infected and HIV-exposed children in sub-Saharan African countries. The review shows that TB is the most researched vaccine-preventable disease in HIV-infected children in various African countries and settings. This is not surprising because of the relationship between TB and HIV infection with respect to the high susceptibility of TB in HIV-infected individuals,[96,97] Other vaccine-preventable diseases like HBV infection, pneumococcal infection, measles, rotavirus gastroenteritis, pertussis and Hib infections were also studied in several African countries. Important vaccine-preventable diseases such as poliomyelitis, diphtheria, tetanus and yellow fever had no eligible studies for inclusion revealing the dearth of incidence and prevalence studies on these diseases. The pooled incidence, prevalence and CFRs reveal there are still high burdens of several vaccine-preventable diseases in sub-Saharan Africa.

According to WHO, the global incidence of TB has been reducing at an average of 2 percent per year.[96] TB incidence has declined in the African region by 4 percent annually since 2013.[96] Southern African countries with the highest prevalence and incidence of HIV such as South Africa, Lesotho, Zimbabwe, Eswatini, Namibia and Zambia had remarkable reductions in TB incidence.[96] Our study shows that TB incidence reduced over time, however, the event per child-year is still high when compared with the End TB strategy goals.[98] The World Health Assembly adopted the resolution known as "*End TB strategy goals"* which is about the global strategy and targets for tuberculosis prevention, care and control after 2015 [98]. In spite of the reduction in TB incidence among children, there are still cases of high incidence in certain countries bearing in mind that many countries in African countries are classified as high-burden.[96] A retrospective cohort study in a very high TB/HIV prevalent region in Nigeria showed a high incidence rate of 21.2/100 per year among children within six months of ART enrollment at a period when others were recording much lower incidence.[17] TB prevalence has fluctuated over time with about 15% of HIV-infected children having the disease at a given point in time. As of 2017, it was estimated that the global CFR was 16% with many African countries recording more than 20%.[96] This rate is also far higher than the End TB Strategy milestone of 10% by 2020.

The pooled HBV infection prevalence among HIV-infected children was 5%, however, a study done in Rwanda in 2010 revealed a seroprevalence of 16%.[73] Ott et al. showed that Sub-Saharan Africa had the highest HBV burden with West African countries having up to 12% hepatitis B surface antigen prevalence among children and adolescents in the 1990s.[99] There has been a reduction within the region largely due to immunisation programmes, however, there is high endemicity in some areas. A systematic review of HBV prevalence in Nigeria from studies conducted from 2000 to 2013 shows that HBV infection ranged from 0.5% to 46.8% with the pooled prevalence estimate for Nigeria being 13.6%.[100]

Our finding shows that the seroprevalence of rotavirus gastroenteritis among African HIV-infected children was 14% although with a small number of included studies. The incidence and CFR of diarrhoea and pneumonia are much higher in low-income than in high-income countries and this is reflected in many African and southeast Asian countries having the highest burden of the diseases.[101] The African region has the highest incidence and total death secondary to diarrhoea and pneumonia with rotavirus and *Streptococcus pneumoniae* being the commonest culprits.[101] Studies have shown that there is still a persistent high incidence of some vaccine-preventable diseases in HIV-infected individuals than non-exposed ones even after the introduction of highly active antiretroviral therapy.[102] The incidence of pertussis is also higher in HIV-exposed and infected children, however, this decreases as the number of vaccine doses uptake increases.[103]

Many African countries with high burdens of HIV are critically lagging in terms of antiretroviral treatment coverage for HIV-infected children.[104] Sub-optimal ART coverage in children will lead to viral load increase, immunosuppression, etc. and a subsequent high burden of various vaccine-preventable diseases. Vaccination coverage in many African countries is still below the expected target.[105] Low uptake of vaccines by African children exposes them to more diseases than children in other regions.

This review revealed research inequalities across the African region regarding the burden of vaccine-preventable diseases studies among HIV-infected and HIV-exposed children. South Africa contributed about half of the included articles with Nigeria and Kenya following with fewer studies. This finding is not different from an earlier study looking at the distribution of

epidemiological studies across Africa.[106] Some of the Eastern and Southern African countries with high HIV prevalence had at least an article included in this study, however, West African countries only had publications from Nigeria and Cote d'Ivoire.

Recommendations

This review has shown that TB is one of the most important vaccine-preventable diseases in Africa with the BCG vaccine conferring protection against severe forms of the disease. However, the same vaccine is contraindicated in immunocompromised children who ironically are susceptible to the disease.[13] The dilemma of BCG use in HIV-exposed children warrants the call for newer and safer vaccines against TB especially in HIV-infected children. African governments and other supporting agencies should ensure that every child has access to routine childhood vaccines. Issues of under-vaccination and vaccine hesitancy should be adequately tackled to ensure better vaccine uptake and reduction in the burden of vaccine-preventable diseases.

The research capacity of African clinicians, researchers and health administrators should be built up for them to conduct basic epidemiological research such as incidence, prevalence, mortality and CFR among HIV-exposed children in various health facilities and communities. Researchers should be encouraged to disseminate their findings to their immediate communities and Departments of Health and to publish their findings in peer-reviewed journals. Established research groups such as Global Burden of Diseases Network should include the burden of vaccine-preventable diseases in HIV-exposed and non-exposed children as part of their regular or annual publications. Other African countries should emulate South Africa in increasing their research activities and outputs with respect to HIV-exposed children.

There is a need to advocate for an equitable share of healthcare budgeting and finance at every level of governance in African countries. This will help in ensuring that there is a fair share of resources for preventive and treatment services such as vaccination and antiretroviral therapy for HIV-exposed children. African countries should, as a matter of urgency, complete the introduction of newer and important vaccines such as rotavirus vaccine, Hib vaccine and pneumococcal vaccine. These should be included as part of their current national immunisation programme schedule[100] According to WHO, the global coverage for both pneumococcal vaccine and rotavirus

vaccines were as little as 44 percent and 25 percent respectively.[105] African countries should be supported in developing vaccine procurement budgets, procurement practices, and capacity development for vaccine planning and advocacy.[107]

Study limitations

This study was limited by several factors beyond the reviewers' control. We planned to review all the vaccine-preventable diseases associated with vaccines included in the national immunisation programme schedule in sub-Saharan Africa, however, we could not find articles that met the eligibility criteria for some of the diseases. Secondly, there was high heterogeneity even with sub-group analysis between included studies, which implies the possibility of other contributory factors associated with the diseases. Some of the studies did not include relevant information such as antiretroviral coverage, CD4 count, viral load, vaccination status and other contributory factors. Thirdly, we could not include many studies because the diagnostic criteria for different vaccine-preventable diseases were not specified and clearly defined.

Conclusions

This systematic review and meta-analysis provide an all-inclusive analysis of the incidence rates, prevalence and CFR of various vaccine-preventable diseases. This study shows that some vaccine-preventable diseases still have high incidence, prevalence and CFRs in HIV-infected and HIV-exposed children. There was also the dearth of research activities on vaccine-preventable disease studies with respect to HIV-infected and HIV-exposed uninfected children in many African countries. The findings are useful in advocating for a more equitable share of healthcare financing especially for preventive services such as vaccination of both HIV-exposed and non-exposed children in order to reduce the burden of vaccine-preventable diseases.

Abbreviations

BCG: Bacillus Calmette–Guérin

DTP: Diphtheria, tetanus and pertussis

EPI: Expanded Programme on Immunisation

GVAP: Global Vaccine Action Plan

Hib: *Haemophilus influenzae* type b

HIV: Human immunodeficiency virus

PCV: Pneumococcal conjugate vaccine

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

RV: Rotavirus

WHO: World Health Organization

Authors' contributions

OOA developed the protocol, search strategy, the data analysis and manuscript preparation. OOA and AA did the screening, study selection and data extraction. OAU and CSW guided the development of this study. All authors were involved in the results interpretation, revision and approval of the final manuscript.

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Appendix

Search strategy - PubMed

Search	Add to builder	Query	Items found
#6	Add	Search ((((#1) AND #2) AND #3) AND #4) AND #5 Sort by: Best Match	1364
#4	Add	Search (newborn* OR bab* OR infan* OR child* OR adolescen* OR teen*) Sort by: Best Match	3843580
#2	Add	Search (tuberculosis OR TB OR poliomyelitis OR polio OR rotavirus OR diphtheria OR tetanus OR pertussis OR pneumococcal OR pneumonia OR measles OR "yellow fever" OR "Hepatitis B" OR "Haemophilus influenza" OR "Hemophilus influenza" OR influenza) Sort by: Best Match	707401
#5	Add	Search (incidence OR prevalence OR mortality) Sort by: Best Match	3171459
#3	Add	Search ("HIV infected" OR "HIV exposed" OR "HIV-infected" OR "HIV-exposed" OR "HIV positive" OR "HIV exposed uninfected") Sort by: Best Match	74539
#1	Add	Search (Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR Cameroon OR "Cape Verde" OR "Central African Republic" OR Chad OR Congo OR "Democratic Republic of Congo" OR DRC OR Djibouti OR "Equatorial Guinea" OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR "Guinea Bissau" OR Guinea OR "Ivory Coast" OR "Cote d'Ivoire" OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR "Republic of the Congo" OR Reunion OR Rwanda OR Senegal OR Seychelles OR "Sierra Leone" OR "Sao Tome and Principe" OR Somalia OR "South Africa" OR "South Sudan" OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR Zambia OR Zimbabwe OR Africa OR "sub Saharan Africa") Sort by: Best Match	558013

CHAPTER 3: Vaccination among HIV–infected, HIV-exposed uninfected and HIV-uninfected children: A systematic review and meta-analysis of evidence related to vaccine efficacy and effectiveness

Olatunji O. Adetokunboh, Duduzile Ndwandwe, Ajibola Awotiwon, Olalekan A. Uthman and Charles S. Wiysonge

Abstract

Evidence-based approaches were used in making recommendations for vaccination against vaccine-preventable diseases for immunocompromised individuals but with limited substantiation. It is therefore paramount to investigate the efficacy and effectiveness of vaccines in HIV-infected and HIV-exposed children in comparison to HIV unexposed children. Web of Science, Cochrane Library, MEDLINE via PubMed and Scopus databases were searched for articles. We conducted a systematic review and meta-analysis with randomised-controlled trials (RCTs), cohort and case-control studies that have efficacy and effectiveness of vaccines in HIV-infected and HIV-exposed children as outcomes. Vaccine efficacy of 9-valent pneumococcal conjugate vaccine (PCV9) in preventing first episodes of invasive pneumococcal disease was 53% among HIV-infected children and 42% among HIV-uninfected children. Efficacy of PCV9 against total vaccine serotype invasive pneumococcal disease was 32% in HIV-infected children and 78% among HIV-uninfected children. Vaccine effectiveness of Bacillus Calmette–Guérin vaccine in preventing tuberculosis in HIV-infected children was zero compared to 59% protection in HIV-unexposed children. Likewise, HIV-uninfected children have better protection against invasive *Haemophilis influenzae* type b (Hib) disease than the HIV-infected children. Effectiveness studies of rotavirus vaccines show that HIV-exposed uninfected children have similar protection against rotavirus gastroenteritis compared to the non-exposed children. Children who are severely

immunosuppressed are poorly protected against invasive pneumococcal diseases. HIV-infected children tend to have lesser vaccine protection against vaccine-preventable diseases when compared to unexposed children. HIV-infected children who are immunocompetent are more likely to have better vaccine protection against vaccine-preventable diseases than those who are immunosuppressed. The overall quality of the observational studies was very low with very little confidence in the effect estimate. The overall quality of evidence for the RCT outcomes was mainly high. This study reveals a dearth of efficacy and effectiveness studies among HIV-infected and exposed children.

***Keywords*:** HIV; vaccine-preventable diseases; sub-Saharan Africa; efficacy; effectiveness

Background

Immunisation is an essential aspect of preventive medicine and critical in reducing morbidity and mortality attributed to vaccine-preventable diseases in children, adolescents and adults.[1] The use of vaccines against various vaccine-preventable diseases is beneficial and an effective measure for protecting different age groups.[2,3] The vaccination rates of children remain insufficient for vaccine-preventable diseases in many developing countries with only 86% of infants vaccinated with three doses of diphtheria-tetanus-pertussis containing vaccine in 2016.[4] Low vaccination uptake rate results in an increase in unvaccinated and under-vaccinated HIV-infected and HIV-exposed children who are more likely to die from preventable diseases than their immunocompetent age mates.[5,6] Several care and treatment guidelines have identified vaccination as a crucial preventive strategy for people living with HIV[7,8] but information on the use of certain vaccines in this population are still scanty.[9]

Experts using evidenced-based approaches on the vaccination of immunocompromised individuals made specific recommendations for vaccination against major vaccine-preventable diseases for these patients but with limited proof.[8] Research gaps were also identified by this group for future investigation. One of these gaps was that of understanding the mediators of vaccine protection, adverse effects and basic aspects of the epidemiology of various vaccine-preventable diseases.[8]

Vaccines stimulate immunity that protects against specific disease-causing organisms. However, the effectiveness of different recommended vaccines in HIV-infected children may be reduced as a result of the decline in vaccine-induced antibodies.[10] The changing pattern of some vaccine-preventable diseases is poorly understood, and this changing pattern and epidemiology makes it important to better understand these diseases because of apparent resurgence and epidemics in future.[11] The suboptimal uptake of vaccines in sub-Saharan Africa coupled with the high HIV burden are risk factors that may facilitate future epidemics.[11,12]

Previous reviews on the efficacy and effectiveness of vaccines in HIV-infected and exposed children were not specific on the vaccine efficacy/effectiveness against disease outcomes and were not conducted as systematic reviews[13,14]. It is paramount to evaluate the available evidence by identifying high-quality literature and investigating the reliability of key findings as they relate to the pre-licensure efficacy and post-licensure effectiveness of vaccines in HIV-infected and HIV-exposed children compared to HIV unexposed children. The findings will provide the needed

evidence to guide healthcare policymakers, guideline developers, vaccinologists and healthcare workers in developing improved long-term vaccination strategies for HIV-infected children. Current and reliable evidence-based data on the efficacy and effectiveness of vaccines in HIV-infected and HIV-exposed children are also vital to inform a better understanding of the prevention and management of vaccine-preventable diseases in these children.

This systematic review and meta-analysis summarised available data from studies which have efficacy or effectiveness of vaccines in HIV-infected and HIV-exposed children as outcomes.

Methods

Search strategy and selection criteria

This review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) guideline.[15] The review was registered with PROSPERO (International prospective register of systematic reviews) (CRD42018095334).

Eligibility criteria

Inclusion criteria

We included randomised-controlled trials (RCTs), cohort and case-control studies that included efficacy or effectiveness of vaccines in HIV-infected in comparison with HIV-exposed or HIV-uninfected children aged ≤ 18 years. The intervention group included those with standard vaccines or dosages while the comparison groups comprised of placebo, non-vaccinated groups, groups that were vaccinated with other control vaccines or other dosages among HIV-infected and HIV-exposed children. For case-control studies, cases were HIV-infected while controls were HIV-exposed uninfected and HIV-uninfected children.

The review planned to include the following licensed vaccines: Bacillus Calmette–Guérin (BCG), hepatitis B vaccine (HBV), oral polio vaccine, inactivated polio vaccine, diphtheria-tetanus-pertussis containing vaccines, *Haemophilus Influenzae* type B vaccine (Hib), pneumococcal conjugate vaccine (PCV), rotavirus vaccine (RV), yellow fever vaccine and measles-containing vaccines. These vaccines were chosen because they are the frequently used childhood vaccines in countries most affected by the HIV epidemic.

Exclusion criteria

Studies having population aged ≥ 18 years old individuals were excluded. We also excluded non-human studies and reviews.

Outcomes

The following were the outcome measures of interest:

1. Clinical and/or confirmed cases of vaccine-preventable diseases of interest.
2. Pooled/reported vaccine efficacy.
3. Pooled/reported vaccine effectiveness.

Data sources

One of the authors, OOA, searched the Web of Science, Cochrane Library, MEDLINE via PubMed and Scopus databases. Reference lists from identified papers and ClinicalTrials.gov trials registry platform were also checked. Relevant World Health Organization (WHO) position papers and documents on vaccines were also scrutinised. There was no language or date restriction.

Selection of studies

Two authors, OOA and DN, independently screened the search results using the abstract titles. They also independently went through the full text of potential studies to determine if the studies meet the inclusion criteria. Discrepancies in the selection process were resolved by consensus.

Data extraction

The two reviewers extracted data from selected articles using a pre-specified form. The extracts included information such as author, journal, year of publication, study design, country of study, participants' characteristics, intervention, comparator, type of vaccine and outcomes. Efficacy and effectiveness data were separately extracted for each vaccine group, target group (i.e. HIV-infected versus HIV-exposed / HIV-uninfected) and study type (interventional versus observational).

Quality assessment

The review quality assessment was guided by the use of Cochrane Collaboration's tool for assessing the risk of bias for included trials and the use of adapted Cochrane tool for observational studies.[16,17] Two authors, OOA and DN, independently assessed the methodological quality of all included studies that met the eligibility criteria. The researchers compared notes for each item and resolved discrepancies through discussion.

Synthesis of data

Synthesis of data was carried out using meta-analysis where applicable. Where meta-analysis was not possible, narrative synthesis was used. We reported the dichotomous outcomes as risk ratios or odds ratio with their corresponding 95% confidence intervals (CI) while continuous outcomes were reported as mean differences.[18] We reported the vaccine effectiveness with the random-effects odds ratio (OR) using the formula: (1 – OR) × 100 while vaccine efficacy was established with risk ratio (RR): (1 – RR) × 100. The efficacy and effectiveness of each vaccine in the intervention arm was compared with that of the control arm. We also planned to use funnel-plot regression to assess publication bias if we had up to ten studies per vaccine type. RevMan statistical software was used to do all calculations, the meta-analysis and to generate the forest plot.[19]

Sensitivity analysis

The certainty of the evidence regarding primary outcomes was determined by the use of the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[20] We planned to assess substantial heterogeneity if I^2 exceeded 50% and the meta-analysis had up to five studies and to perform subgroup analyses using pre-specified potential sources of heterogeneity such as: type of comparison (i.e. placebo or no vaccine), blinding of patients (only for trials); blinding of outcome assessors; and overall methodological quality.

Results

Description of included studies

The flow diagram in Figure 1 shows the studies identified and selected for this review. We identified 725 publications through databases and clinical trial registry search with 479 studies after removal of duplicates. A total of 14 publications were included in this review. These publications comprise five RCTs,[21-25] six case-control studies,[26-31] one cohort study[32] and two cross-sectional studies[33,34]. Three of the included studies were publications from a particular South African trial that reported different vaccine efficacy outcomes.[21,23,24] The included studies were published from 1993 to 2017. All the included studies were conducted in sub-Saharan Africa with ten publications from South Africa, one each from Malawi, Angola and Zambia, and one multinational study conducted in Mali, Kenya and Ghana.

By outcomes, three studies reported rotavirus vaccine outcomes, six studies reported on pneumococcal vaccine, one study reported on Hib vaccine, two studies on BCG and two studies reported on HBV vaccines (Table 1). Two studies compared vaccine strains with placebo among HIV-infected children while three studies compared vaccine strains with placebo among HIV-infected and HIV-unexposed children. Six studies compared HIV-infected children with HIV-unexposed children, while two studies compared HIV-exposed and uninfected children with HIV-unexposed children. In total, 66,220 children in comparative studies were involved in the included studies. The vaccine schedule and doses for the included studies were according to various national programme except for Madhi 2007[23] participants who were followed up for five years. Antiretroviral therapy (ART) usage varied between 22.5% and 67.0% among the HIV-infected children.

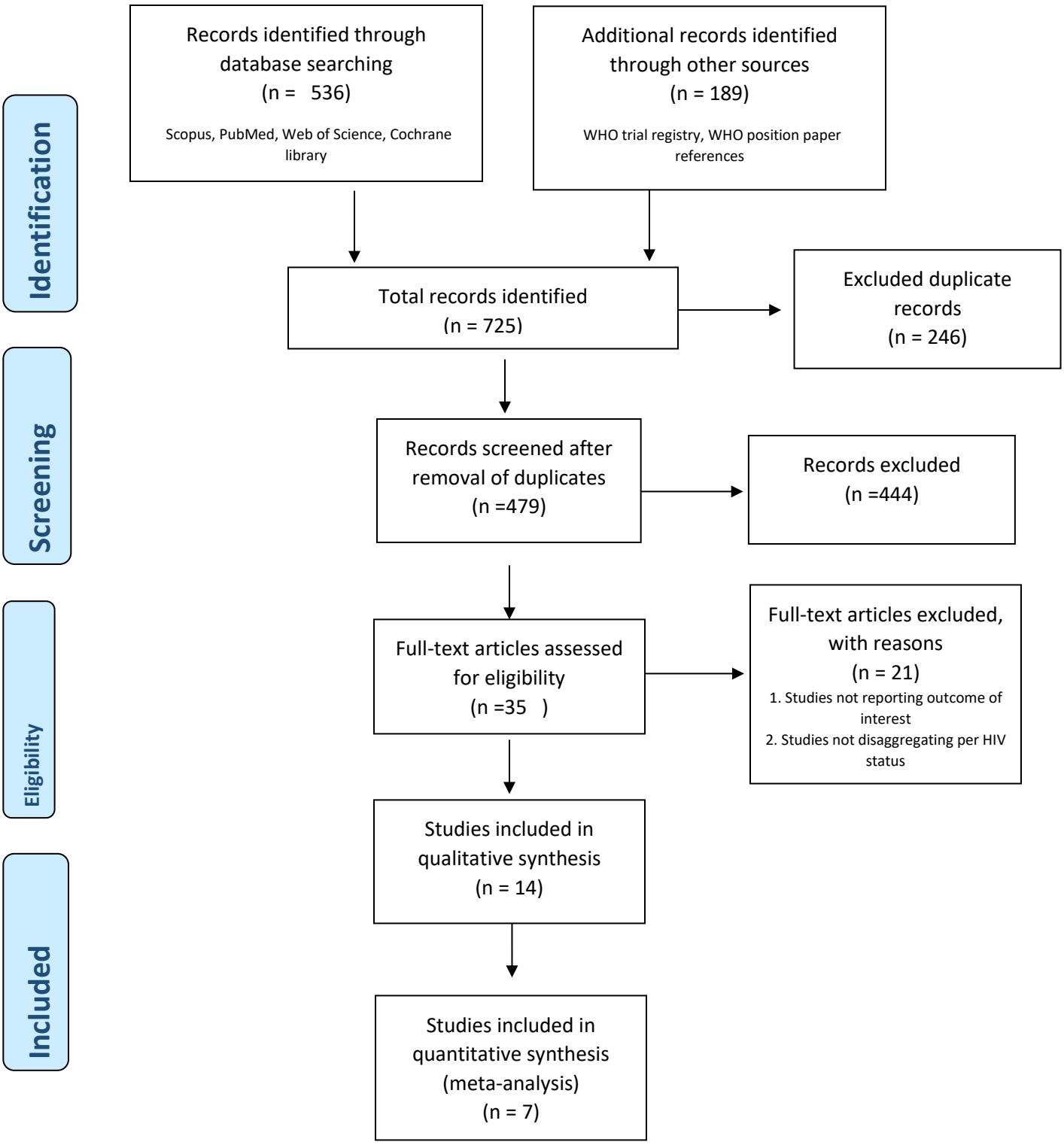

Figure 1: Flow diagram of the search and selection process for this review

Table 1: Characteristics of included studies

Participants						Intervention					Control				
1st Author & Year	**Study period**	**Study design**	**Study country**	**Sample size (n=)**	**Participant age range**	**HIV status**	**% on ART**	**CD4 % or count**	**Age (median or mean)**	**Vaccine strain**	**HIV status**	**% on ART**	**CD4 % or count**	**Age (median or mean)**	**Vaccine strain**
Beghin 2017[33]	2014	Cross-sectional study	South Africa	291	5-15y	HI	NR	NR	9.1y	HBV	HU	-	-	9.0y	HBV
Cohen 2017[27]	2012-2014	Case-Control	South Africa	1716	≥6w	HI	58%	-	48-53w	PCV13	HU	-	-	36-37w	PCV13
Bar-Zeev 2016[31]	1997-2007	Case-control	Malawi	919	<5y	HEU	-	-	NA	RV	HU	-	-	NA	RV
Van-Dunem 2015[28]	2005-2006	Case-control	Angola	902	18m - 13y	HI	67%	NR	4.83y	BCG Connaught	HI	61%	NR	3.50y	-
Cohen 2014[26]	2010-2012	Case-Control	South Africa	1395	≥8w	HI	46%	NR	52-54w	PCV7	HU	-	-	38-39w	PCV7
Groome 2014[29]	2010-2012	Case-control	South Africa	1195	18w-23m	HEU	-	-	9m	Monovalent human RV	HU	-	-	10 m	Monovalent human RV
Feikin 2012[22]	2007-2009	RCT	Kenya, Ghana, Mali	29	4-12w	HI	NR	NR	17.1w	PRV	HI	NR	NR	17.0	Placebo
Steele 2011[25]	2005-2008	RCT	South Africa	100	6-10w (at dose 1)	HI	62%	2074	7w	RIX4414	HI	52%	2022	7w	Placebo
Simani 2008[34]	2003-2004	Cross-sectional study	South Africa	303	5-24m	HI	NR	NR	8.7m	HBV	HU	-	-	11.9m	HBV
Madhi 2007[23]	2001 - 2005	Post RCT	South Africa	39836	5.57-5.80y	HI	22.5%	493; 627	5.80y; 5.68y	PCV9	HU	-	-	5.68y; 5.57y	Placebo
Madhi 2005[24]	1998 - 2001	RCT	South Africa	39836	28-84d	HI	NR	NR	NA	PCV9	HU	-	-		Placebo
Klugman 2003[21]	1998 - 2001	RCT	South Africa	39836	28-84d	HI	NR	NR	NA	PCV9	HU	-	-	7w	Placebo
Madhi2002[32]	1997-2000	Cohort	South Africa	19267	<1y	HI	NR	NR	NR	HibCV	HU	-	-	NR	HibCV
Bhat 1993[30]	1991	Case-control	Zambia	270	1m-14y	HI	NR	NR	NR	BCG	HU	NR	NR	NR	BCG

HI - HIV-infected; HEU - HIV-exposed uninfected; HU - HIV-uninfected; NR- not reported; m- month; w – week; d- day; y- year; RCT – randomized controlled trial; HBV – Hepatitis B vaccine; HibCV- *haemophilus influenzae* b conjugate vaccine; PCV7 – 7-valent pneumococcal conjugate vaccine; PCV9 – 9-valent pneumococcal conjugate vaccine; PCV13 – 13-valent pneumococcal conjugate vaccine; BCG - Bacillus Calmette–Guérin; PRV – pentavalent rotavirus

Quality of evidence

Risk of bias assessment of individual studies

Risk of bias assessment of the included studies is summarised separately for RCTs (Figure 2) and observational studies (Figure 3). All the studies except one contained at least one domain classified as high risk of bias or with no clear information.

Randomised trials

Only three RCTs were assessed.[21,22,25] Klugman 2003[21] was used in assessing two other included studies[23,24] since the study participants were the same for all three publications. There was insufficient information on random sequence selection in majority of the studies as shown in Figure 4. Allocation concealment, performance and detection biases were low for most of the studies. Steele 2011[25] had unclear risk of bias for most of the domains. Feikin 2012[22] had high risk of bias for reporting and other bias domains for not reporting all the pre-specified primary outcomes and having numerous limitations.

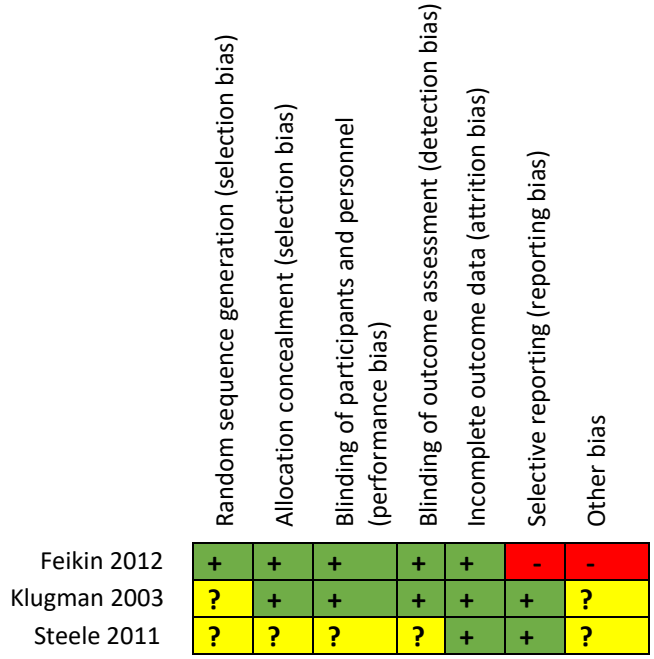

Figure 2: Risk of bias summary for the included randomised-controlled trials

Observational studies

All the observational studies had one high or unclear risk of bias across different domains except one study.[21,26,27,29-34] The reasons for the high risk of bias varied and ranged from the use of hospital control instead of community controls, imbalanced missing participant numbers and unmeasured confounders (Figure 5).

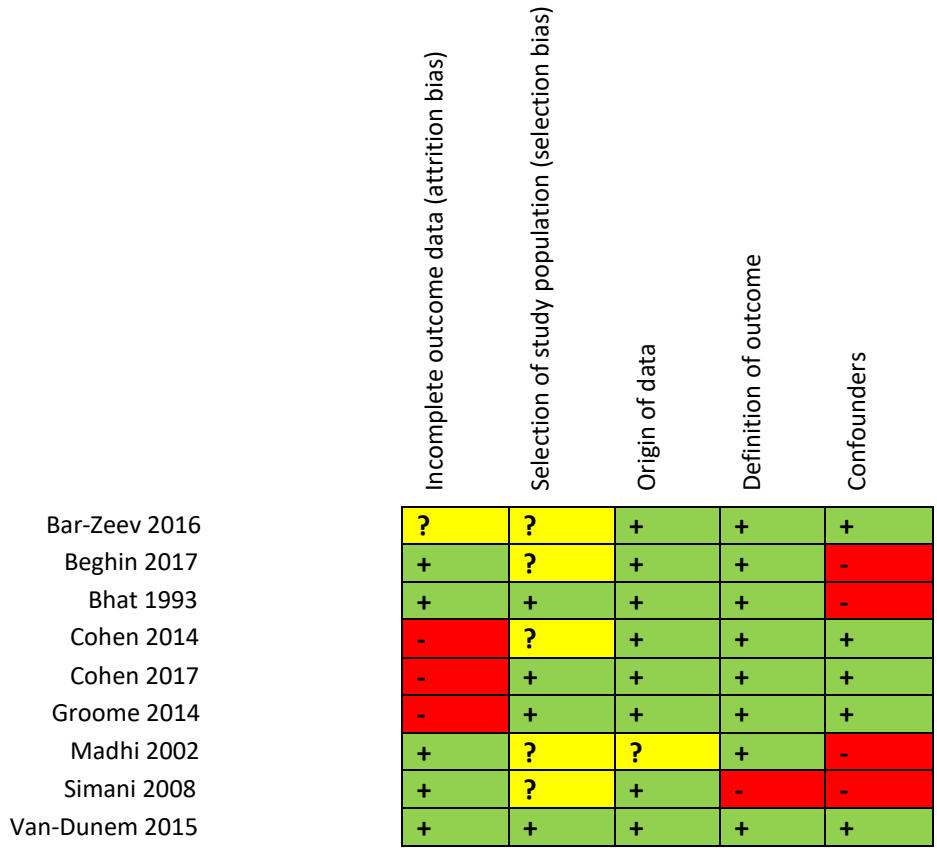

Figure 3: Risk of bias summary for the included observational studies

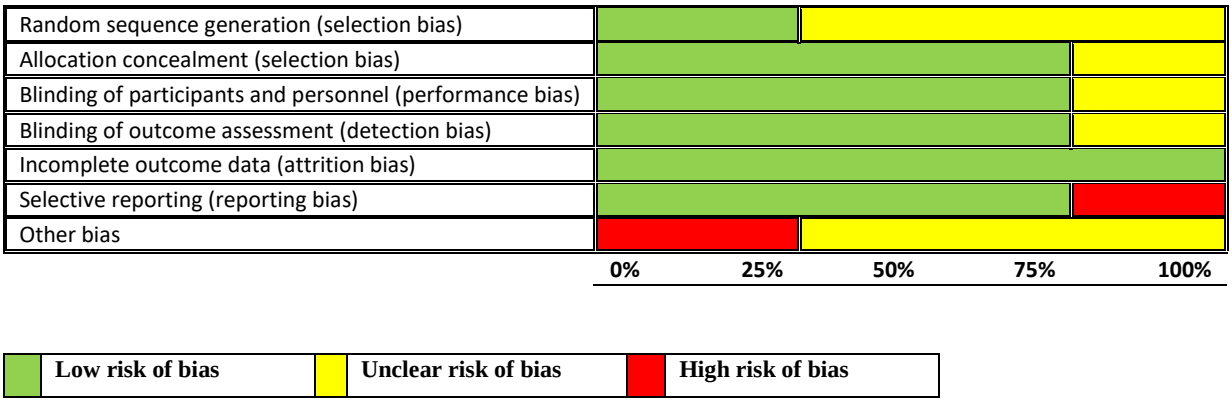

Figure 4: Risk-of-bias graph: review authors' judgements about each risk-of-bias item presented as percentages across all included studies

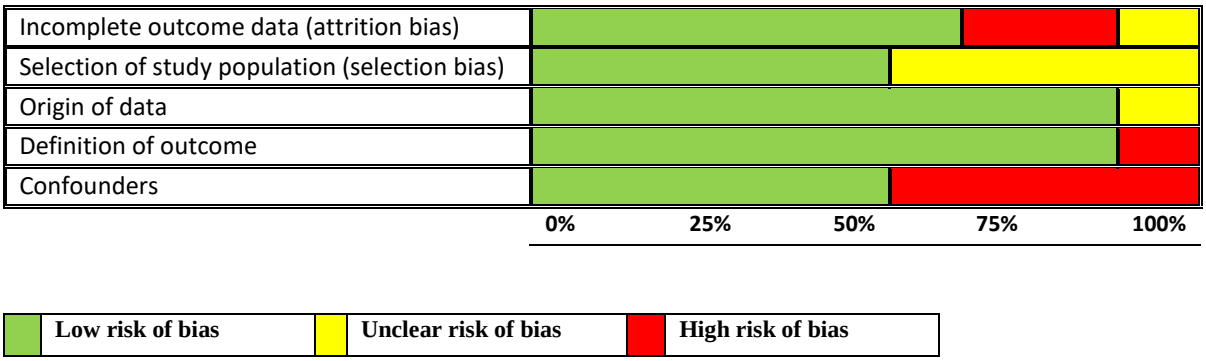

Figure 5: Risk of bias graph: review authors' judgements about each risk-of-bias item presented as percentages across all included studies

The quality of the evidence was also evaluated using the GRADE approach. Overall quality for the observational studies was very low with very little confidence in the effect estimate. The overall quality of evidence for the RCT outcomes was mainly high. This makes our confidence in the effect estimate to be moderate. With these results, we are confident that the true effect lies close to that of the estimate of the effect and does not require further research. See Summary of findings in Tables 2 and 3.

Table 2: Summary of findings table for the efficacy of vaccines in HIV-infected, HIV-exposed and HIV-uninfected children (RCTs)

Patient or population: HIV-infected, HIV-exposed and HIV-uninfected children

Intervention: Vaccines

Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with vaccines			
HI/PRV/RVGE	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 2.81** (0.12 to 63.83)	29 (1 RCT)	⨁⨁◯◯ LOW [a]
HI/RIX4414/RVGE	80 per 1,000	**80 per 1,000** (21 to 270)	**HR 1.00** (0.26 to 3.78)	100 (1 RCT)	⨁⨁⨁◯ MODERATE [a]
HI/PCV9/severe pneumonia	280 per 1,000	**233 per 1,000** (205 to 266)	**RR 0.83** (0.73 to 0.95)	2577 (1 RCT)	⨁⨁⨁⨁ HIGH
HU/PCV9/severe pneumonia	36 per 1,000	**32 per 1,000** (28 to 36)	**RR 0.89** (0.80 to 1.00)	37259 (1 RCT)	⨁⨁⨁⨁ HIGH
HI/PCV9/Total IPD	26 per 1,000	**18 per 1,000** (11 to 30)	**RR 0.68** (0.40 to 1.14)	2577 (1 RCT)	⨁⨁⨁⨁ HIGH
HU/PCV9/Total IPD	1 per 1,000	**0 per 1,000** (0 to 0)	not estimable	37259 (1 RCT)	⨁⨁⨁⨁ HIGH

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanation: a. A wide confidence interval of the estimate

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 3: Summary of findings table for the efficacy of vaccines in HIV-infected, HIV-exposed and HIV-uninfected children (Observational studies)

Patient or population: HIV-infected, HIV-exposed and HIV-uninfected children

Intervention: Vaccine

Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with vaccine			
HBV/Hepatitis B vaccine	3 per 1,000	**18 per 1,000** (3 to 103)	**OR 6.02** (0.93 to 38.83)	594 (2 observational studies)	⨁◯◯◯ VERY LOW [a,b]
HI/BCG/Tuberculosis	**Low**		**OR 1.00** (0.22 to 4.56)	36 cases 18 controls (1 observational study)	⨁◯◯◯ VERY LOW [b,c]
	0 per 1,000	**0 per 1,000** (0 to 0)			
HU/BCG/Tuberculosis	**Low**		**OR 0.41** (0.18 to 0.92)	60 cases 116 controls (1 observational study)	⨁◯◯◯ VERY LOW [b,c]
	0 per 1,000	**0 per 1,000** (0 to 0)			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio

Explanations: a. Confounders were not taken into account and unclear about the selection of study participants; b. A wide confidence interval around the estimate of the effects; c. Confounders not taken into account

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Vaccine efficacy for vaccine-preventable diseases outcomes

Table 4 shows reported risk ratios and vaccine efficacy for vaccine-preventable diseases outcomes in vaccinated versus non-vaccinated participants in trials for several outcomes. Vaccine efficacy of 9-valent pneumococcal conjugate vaccine (PCV9) vs. placebo in preventing first episodes of invasive pneumococcal disease was 53% (95% CI 21 - 73) among HIV-infected children and 42% (95% CI -28 - 75) among HIV-uninfected children. Efficacy of PCV9 against total vaccine serotype invasive pneumococcal disease was 32% (95% CI -14 - 60) in HIV-infected and 78% (95% CI 34 - 92) among HIV-uninfected children.

There was similar response among HIV-infected children who were given RIX4414 vaccine and those given placebo for prevention of acute rotavirus diarrhoea (RR= 1.00; 95% CI 0.26 - 3.78) (Table 5). The subset of HIV-infected children in a particular trial that compared pentavalent rotavirus vaccine (PRV) and placebo showed RR of 2.81 (95% CI 0.12 - 63.83) (Table 5).

Vaccine effectiveness for vaccine-preventable diseases outcomes

Table 6 reports vaccine effectiveness for vaccine-preventable diseases outcomes in vaccinated versus non-vaccinated participants in observational studies for different outcomes. The pooled odds ratio (OR) of two studies on the effectiveness of HBV vaccines between HIV-infected and HIV-uninfected children was OR = 6.02 (95% CI 0.93 - 38.83*;* I^2 = 0.00%) (Table 5; Figure 6). Vaccine effectiveness of BCG vaccine in preventing tuberculosis in HIV-infected children was zero compared to 59 percent protection in HIV-unexposed children (Table 5). Likewise, HIV-uninfected children have better protection against invasive Hib disease than the HIV-infected children (97% versus 44%). Effectiveness studies of rotavirus vaccines show that HIV-exposed uninfected children have similar protection against rotavirus gastroenteritis comparable to the non-exposed children. The adjusted vaccine effectiveness of PCV13 against invasive pneumococcal disease was 78% (95% CI 46 to 91) in HIV-uninfected children, 17% (95% CI –304 - 80) in HIV-infected and –104% (95% CI –1433 - 73) among HIV-infected children who were severely immunosuppressed.

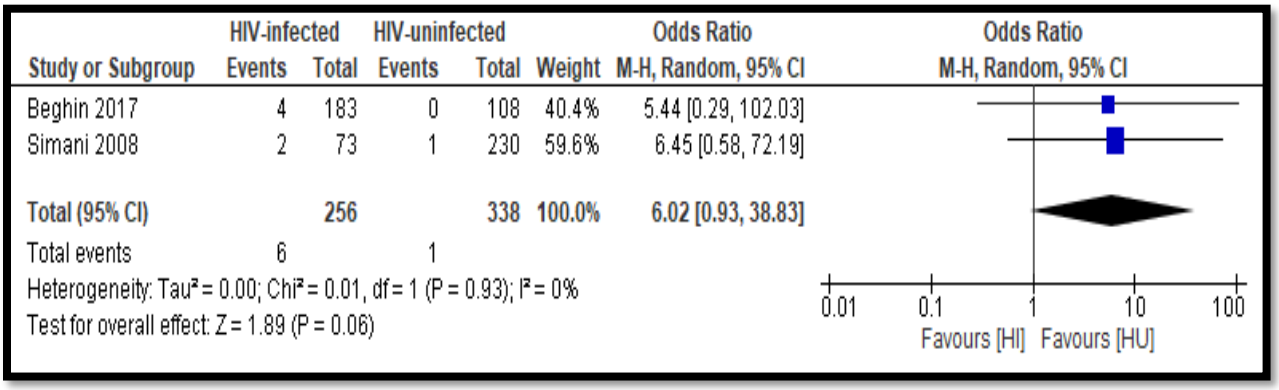

Figure: 6: Forest plot of comparison: Vaccine effectiveness comparing HIV-infected and HIV-uninfected - Hepatitis B vaccine, outcome: HBV/Hepatitis B vaccine

Table 4: Reported risk ratios and vaccine efficacy for vaccine-preventable diseases outcomes in vaccinated vs. non-vaccinated participants in randomised-controlled trials

Study ID (year)	Doses	Experimental recipients/vaccine	Control recipients/vaccine	Vaccine efficacy (%)	Disease of interest
Klugman 2003[21]	3	HI/PCV9	HI/placebo	53 (21 to 73)	First episodes of invasive pneumococcal disease
Klugman 2003[21]	3	HU/PCV9	HU/placebo	42 (-28 to 75)	
Klugman 2003[21]	3	HI/PCV9	HI/placebo	13 (-7 to 29)	First episodes of radiologically confirmed pneumonia
Klugman 2003[21]	3	HU/PCV9	HU/placebo	20 (2 to 35)	
Madhi 2005[23]	3	HI/PCV9	HI/placebo	17 (5, 27)	WHO-defined severe pneumonia
Madhi 2005[23]	3	HU/PCV9	HU/placebo	11 (1, 20)	
Madhi 2007[24]	3	HI/PCV9	HI/placebo	32 (-14, 60)	Total vaccine serotype invasive pneumococcal disease
Madhi 2007[24]	3	HU/PCV9	HU/placebo	78 (34, 92)	
Steele 2011[25]	3	HI/ RIX4414	HI/placebo	0 (-278, 74)	Acute rotavirus diarrhoea
Feikin 2012[22]	3	HI/PRV	HI/placebo	-181 (-6283, 88)	

Table 5: Calculated vaccine efficacy and effectiveness for various vaccine outcomes

Outcomes	Number of studies	Experimental group	Control group	Relative effects	Study references
Hepatitis B virus infection	2	HI/HBV	HU/HBV	OR = 6.02 (0.93, 38.83)	33,34
Rotavirus gastroenteritis	1	HI/PRV	HI/Placebo	RR = 2.81 (0.12, 63.83)	22
Rotavirus gastroenteritis	1	HI/RIX4414	HI/Placebo	RR = 1.00 (0.26, 3.78)	25
Severe pneumonia	1	HI/PCV9	HI/Placebo	RR = 0.83 (0.73, 0.95)	23
Severe pneumonia	1	HU/PCV9	HU/Placebo	RR = 0.89 (0.80, 1.00)	23
Total Invasive Pneumococcal Disease	1	HI/PCV9	HI/Placebo	RR = 0.68 (0.40, 1.14)	24
Total Invasive Pneumococcal Disease	1	HU/PCV9	HU/Placebo	RR = 0.22 (0.08, 0.66)	24
Tuberculosis	1	HI/BCG	HI/Unvaccinated	OR = 1.00 (0.22, 4.56)	30
Tuberculosis	1	HU/BCG	HU/Unvaccinated	OR = 0.41 (0.18, 0.92)	30

BCG- Bacillus Calmette–Guérin vaccine; HI- HIV-infected; HU- HIV-uninfected; HBV – Hepatitis B virus; PCV – pneumococcal conjugate vaccine; PRV- pentavalent rotavirus; OR- odds ratio; RR- risk ratio

Table 6: Reported vaccine effectiveness against vaccine-preventable diseases in observational studies

Study ID (year)	Vaccine type	Doses	HIV status	Vaccine effectiveness (%)	Adjusted vaccine effectiveness (%)	Disease of interest
Bhat (1993)[30]	BCG	1	HI	0 (−360 to 78)		Tuberculosis
		1	HU	59 (8 to 82)		
Madhi (2002)[32]	HibCV	3	HI	43.9 (76.1 to 82.1)		Invasive Hib disease
		3	HU	96.5 (74.4 to 99.5)		
Groome (2014)[29]	Monovalent RV	2	HEU		58% (16 to 79)	Acute rotavirus diarrhoea
		2	HU		52% (23 to 70)	
Cohen (2014)[26]	PCV7	≥3	HI	43 (−108 to 85)	57 (−371 to 96)	Invasive pneumococcal disease
		≥3	HU	57 (−100 to 91)	90 (14 to 99)	
Van-Dunem (2015)[28]	BCG Connaught	1	HI	8 (−26 to 32)	30 (−75 to 72)	Tuberculosis
Bar-Zeev (2016)[31]	Monovalent RV	2	HEU		42.2% (−106.9 - 83.8)	Acute rotavirus diarrhoea
		2	HU		60.5% (13.3–82.0)	
Cohen (2017)[27]	PCV13	≥2	HI (overall)	26% (–98 to 72)	17% (–304 to 80)	Invasive pneumococcal disease
		≥2	HI with severe immunosuppression	–42% (–723 to 76)	–104% (–1433 to 73)	
		≥2	HI with no severe immunosuppression	75% (–31 to 95)	66% (–94 to 94)	
		≥2	HU (overall)	83% (61 to 92)	78% (46 to 91)	
		≥2	HEU	91% (60 to 98)	87% (38 to 97)	

Discussion

The findings of this systematic review show that various routine vaccines have varying levels of protective efficacy and effectiveness against different vaccine-preventable diseases among HIV-infected and HIV-exposed children. This study demonstrates that PCV9 and 13-valent pneumococcal conjugate vaccine (PCV13) vaccines are efficacious in preventing invasive pneumococcal disease, radiologically confirmed pneumonia and severe pneumonia.[21] PCV9 also reduced the incidence of antibiotic-resistant invasive and vaccine serotype pneumococcal disease in both HIV-infected and uninfected children.[21] However, PCV vaccines are less efficacious in preventing total vaccine serotype invasive pneumococcal disease in HIV-infected children compared to HIV-uninfected children.[22] Cohen et al.show that HIV-infected children have less protection against invasive pneumococcal disease when vaccinated with doses of PCV13.[27] HIV-infected children with severe immunosuppression are unprotected against invasive pneumococcal disease even at higher vaccine doses.[27]

Vaccine-efficacy studies show that RIX4414 and PRV do not have protective activities against acute rotavirus diarrhoea in HIV-infected children.[22,25] The poor efficacy of PRV in children living with HIV may largely be as a result of the small sample size of the HIV-infected children subset in a Kenyan trial.[22] However, Feikin et al. show that PRV efficacy against severe rotavirus gastroenteritis was 63.9% (95% CI −5.9-89.8) in a study with a large number of both HIV-infected and uninfected children in the second year of life and 83% in the first year of life. The study on RIX4414 shows that there was no significant difference in the incidence of rotavirus diarrhoea in the vaccine and placebo groups thereby deducing that the vaccine did not have any significant protective effect in HIV-infected children.[23] Monovalent rotavirus vaccines provided at least 40 to 60 percent protection against acute rotavirus gastroenteritis in both HIV-exposed uninfected and HIV-unexposed children but the effectiveness in HIV-infected children is not yet known.[29,32]

Vaccine-effectiveness studies show that Hib conjugate vaccine provided more than 50% protection against invasive Hib disease in HIV-uninfected children when compared to HIV-infected children.[30] Hib conjugate vaccine has a protective effect of 83% in preventing overall invasive Hib disease in among HIV-infected children and very useful.[32] A study among Zambian children shows that BCG has 59 percent protective effect against tuberculosis in HIV-uninfected children and none in HIV-infected children.[30] The findings of a case-control study among Brazilian children

also allude to the fact that BCG does not protect against tuberculosis in immunodeficient HIV-infected children.[26]

Studies have shown that most of the vaccines included in this review are safe for use in all categories of children.[1,21,25,35,36] A number of reviews and safety studies on several routine vaccines among HIV-infected/exposed children and HIV-unexposed children show that there was no significant difference in these groups of children with respect to adverse events, serious adverse events and death.[37-39] Most of the serious adverse events and deaths were not vaccine related. Reviews also show that immune responses to primary vaccination in HIV-infected children were less likely compared to HIV-unexposed and HIV-exposed children and may require booster doses.[37,38,39]

There is a dearth of vaccine efficacy and effectiveness studies against vaccine-preventable diseases among HIV-infected and exposed children. This review shows that some efficacy studies have been done for PCV, BCG, rotavirus vaccines and Hib vaccines in HIV-infected children. There is a need to close the knowledge gap in relation to pre-licensure vaccine efficacy and post-licensure vaccine effectiveness against key vaccine-preventable diseases among these groups of children. Closing the gaps will entail conducting efficacy and effectiveness studies for several routine vaccines in HIV-infected and exposed children.[13] Use of BCG vaccines in HIV-infected children can lead to disseminated tuberculosis hence it is contraindicated in immunocompromised children. It is therefore, not advisable to do a BCG vaccine-efficacy study in these children.[40] BCG is safe in immunocompetent infants, however, immunocompromised infants are at high risk of developing disseminated BCG disease.[41]

Effectiveness research is essential and relevant for decision making by policy makers, treatment guideline researchers, vaccine development researchers and healthcare providers.[42] Vaccine-efficacy research is essential in making the necessary decisions to achieve the goals of the Global Health 2035 Grand Convergence.[43] The WHO has already recommended many vaccines for use in immunocompromised children especially those who have had exposure to HIV, however, most of these recommendations were made without specific vaccine-efficacy and effectiveness studies conducted in this population but rather from research findings on immunocompetent children or by using safety and immunogenicity studies.[1,40] Knowing the vaccine efficacy and effectiveness

against specific diseases will help steer guideline development and the need for better vaccines if the level of protection is low.

Strengths of this systematic review and meta-analysis are the comprehensive search conducted in several databases and the inclusion of several routine vaccines. This review also compiled evidence on efficacy and effectiveness of vaccines that could be of use in HIV-infected and HIV-exposed children especially in sub-Saharan Africa. Lack of direct comparisons between HIV-infected and unexposed children with respect to various clinical cases of vaccine-preventable diseases limited straightforward grading of the evidence for clinical case outcomes. Only seven studies could be included in the meta-analysis due to lack of data information on some clinical outcomes and reported efficacy and effectiveness as described by the authors.

Conclusions

Efficacy and effectiveness studies on vaccination exhibit possibilities for direct and indirect protection against various vaccine-preventable diseases among HIV-infected and HIV-exposed children. HIV-infected children tend to have less protection against vaccine-preventable diseases when compared to unexposed children. HIV-infected children who have access to antiretroviral therapy and are immunocompetent are more likely to have better vaccine protection against vaccine-preventable diseases than the immunosuppressed ones. There is also a need to bridge the knowledge gap on vaccine efficacy and effectiveness of several routine vaccines in HIV-infected and exposed children. This study reveals that only a few vaccine-efficacy and effectiveness studies have been done in HIV-infected and exposed children previously.

Abbreviations

BCG: Bacillus Calmette–Guérin

CI: Confidence intervals

DTP: Diphtheria, tetanus and pertussis

HI: HIV-infected

HU: HIV-uninfected

Hib: *Haemophilus influenzae* type b

HIV: Human immunodeficiency virus

PCV9: 9-valent Pneumococcal conjugate vaccine

PCV13: 13-valent pneumococcal conjugate vaccine

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

PRV: Pentavalent rotavirus

RCT: Randomised controlled trials

RV: Rotavirus

WHO: World Health Organization

Authors' contributions

OOA developed the protocol, search strategy, data analysis and manuscript preparation. OOA and DN did the screening, study selection and data extraction. OAU and CSW guided the development of the study. All authors were involved in the interpretation of results, revision and approval of the final review manuscript.

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CHAPTER 4: Effect of maternal HIV status on vaccination coverage among sub-Saharan African children: A socio-ecological analysis

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Abstract

We investigated the relationship between maternal HIV status and uptake of the full series of three doses of diphtheria-tetanus-pertussis containing vaccines (DTP3) in sub-Saharan African children. We used data obtained from demographic and health surveys conducted in sub-Saharan Africa. We conducted a meta-analysis and calculated pooled odds ratios (OR) for the association between maternal HIV status and DTP3 vaccination status for each country. A total of 4,187 out of 5,537 children of women living with HIV received DTP3 (75.6%), compared to 71,290 of 113,513 (62.8%) children of HIV-uninfected women. National DTP3 coverage among children of HIV-infected women varied between 24% and 96% while among children of HIV-uninfected women it was between 26% and 92%. Overall pooled result showed no significant difference in DTP3 coverage between the two groups (OR = 1.05; 95% confidence interval 0.91 - 1.22), with statistically significant heterogeneity (Chi^2 = 91.63, P = 0.000, I^2 = 71.6%). There was no association between DTP3 coverage and maternal HIV status in sub-Saharan Africa. However, DTP3 coverage for both HIV-exposed and non-exposed children were below the required target. Meta-regression revealed no significant association between DTP3 coverage and country characteristics (e.g. HIV prevalence among women, antiretroviral therapy coverage, gross domestic product per capita, human development index, adult literacy rate and sub-region). Improved prevention of mother-to-child transmission services might have contributed to some extent to the higher DTP3 vaccination coverage among the HIV-exposed children. There is also a need to address barriers impeding the uptake of vaccination among HIV-exposed and non-exposed children.

***Keywords*:** Immunisation coverage; HIV; vaccine-preventable diseases; sub-Saharan Africa; demographic and health surveys

Introduction

Human immunodeficiency virus (HIV) infection remains a major public health challenge and a foremost cause of disability-adjusted life years in sub-Saharan Africa.[1,2] Sub-Saharan Africa accounts for about 75% of the global burden of HIV.[3,4] It is estimated that approximately 1.5 million HIV-infected children live in sub-Saharan African countries and these countries also account for the highest burden of vaccine-preventable diseases.[4,5]

Vaccination has been demonstrated to be a cost-effective and beneficial public-health intervention in protecting children.[6] Vaccination is essential in HIV-infected individuals because of their increased risk of developing various infectious diseases due to their defective immune systems.[7] Unfortunately, the coverage of routine vaccinations for children in many African countries is still low and inadequate to meet the Global Vaccine Action Plan (GVAP) targets.[8–10] Studies have also shown that HIV-exposed and infected children have significantly increased risk of morbidity and mortality from various vaccine-preventable diseases when compared with HIV-unexposed and uninfected children.[11,12] The low vaccination coverage may result in increased susceptibility to infection by various vaccine-preventable diseases among the infants of women living with HIV.

Exploring the effect of maternal HIV status on childhood vaccination among children in sub-Saharan Africa is critical to inform vaccine-preventable disease-prevention strategies. A study on vaccination coverage in HIV-infected patients shows that patients with a specific indication for a given vaccine have better vaccination coverage, however, adherence to vaccination guidelines is not likely to be a determinant for vaccination among the HIV-infected patients.[13] Research is needed to close the evidence gap with respect to the coverage of childhood vaccination and the impact of maternal HIV status.[13]

This study examined the vaccination coverage of the three doses of diphtheria-tetanus-pertussis containing vaccines (DTP3) among children with respect to the maternal HIV status. The study also assessed the relationship between various country-level characteristics and the coverage of DTP3 among sub-Saharan African children by pooling available survey data.

Methods

Data

The study used data obtained from DHS conducted in sub-Saharan African countries.[14] The DHS data are cross-sectional and population-based representative sample surveys of households. The sampling frame for each survey is made up of a list of enumeration areas covering the whole country. The surveys involve a two-stage sample design with standardised questionnaires administered to the selected participants in each country. These were implemented by respective National Ministry of Health or Research/Statistical agencies with technical support from MEASURE DHS, ICF International, Calverton, Maryland, USA and with funding from various development partners such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, the United States Agency for International Development etc. The included countries were selected based on the availability of the DHS surveys with data on the uptake of three doses of DTP and whether the mother had had an HIV test as of November 2017. Based on these criteria, 27 sub-Saharan African countries were included namely: Angola, Burkina Faso, Burundi, Cameroon, Chad, Democratic Republic of the Congo, Cote d'Ivoire, Ethiopia, Gabon, The Gambia, Ghana, Guinea, Kenya, Lesotho, Liberia, Malawi, Mali, Namibia, Niger, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, Swaziland, Togo, Zambia and Zimbabwe.

Eligible women within the age range of 15-49 years old were encouraged during the interview to test for HIV voluntarily.. The trained interviewers then collected finger-prick, dried blood-spot specimens for HIV testing. The sample collection and analysis protocol is based on the anonymous linked protocol. The DHS programme protocol allows the merging of results of the HIV test with other data collected per each respondent's questionnaires.

Main variable

The main variable was the uptake of three doses of diphtheria-tetanus-pertussis containing vaccines among children aged 12-23 months at any time before the survey; as reported on their vaccination cards or by their mothers during interviews. The mother's HIV status was recorded as either HIV seropositive or seronegative.

Country-level variable

Country-level data were matched within the same time frame when DHS were conducted using various reports published by the United Nations Development Programme,[15] World Bank[16] and

Joint United Nations Programme on HIV/AIDS (UNAIDS).[4] The country-level characteristics included in this study were percentage coverage of pregnant women who received antiretroviral drugs for prevention of mother-to-child transmission of HIV (PMTCT), HIV prevalence, childhood vaccination coverage level, gross domestic product (GDP) per capita, adult literacy rate, and human development index (HDI). We divided the country-level variables into low, medium or high categories in order to provide results that were more easily interpretable for policy purposes.

These country-level variables were some of the maternal and developmental factors that are likely determinants of vaccination coverage especially among HIV-exposed.[15,16] We expected the study to show the associations between vaccination coverage and country-level factors by identifying differences in country characteristics that might be responsible for variations in the coverage in sub-Saharan Africa.

Ethical considerations

This study used existing DHS data from various countries with the study data identifier information removed. The surveys were approved by the Institutional Review Boards of the ICF International, and the Centers for Disease Control and Prevention, Atlanta, USA and by the National Ethics Committees of the included countries. All the study respondents gave informed consent for participation and the confidentiality of the collected information was maintained.

Statistical analysis

Meta-analysis

We calculated odds ratios (OR) for the association between maternal HIV status and childhood DTP3 vaccination status for each country. The DerSimonian-Laird method (random-effects model)[17] was used to calculate pooled odds ratio across countries. The study is an individual patient data meta-analysis. We evaluated the homogeneity of the results by means of the Chi-square test and used the I^2 to describe the percentage variation across countries.[18-20] We explored substantial heterogeneity (I^2>50%) by subgroup analysis.

To investigate sources of heterogeneity, sub-group analysis was conducted using the DerSimonian-Laird method. The sub-groups were designed using the following categories:

i. GDP (low-income: ≤ $1,025; middle-income: $1,026 - $12,475). GDP middle class consists of both lower-middle and upper-middle classes.
ii. HDI (low: ≤0.549; medium: 0.550 – 0.770), based on the classification by United Nations Development Programme.
iii. Coverage of pregnant women who received antiretroviral drugs for PMTCT (low: ≤ 50.0; high: ≥ 50.1).
iv. HIV prevalence aged 15-49 years old (low: ≤ 10.0; high: ≥ 10.1). The cut off of 10.0 was used based on the range of the prevalence for different countries included in this study.
v. Adult literacy rate (low: ≤ 50.0; high: ≥ 50.1).
vi. Sample size (small size if ≤5000 or large size if ≥ 5001). The cut-off point of 5000 was before it is the average sample size for the participating countries.
vii. Sub-region (Central/Eastern, Southern and Western Africa).
viii. Year of the survey (2003-2010 and 2011-2016). The cut-off point for the years of survey was 2010 because 2011 marks the start of the Global Vaccine Action Plan.

We performed leave-one-country-out sensitivity analysis to determine the stability of the results. This analysis evaluated the influence of individual country results by estimating the weighted average odds ratio in the absence of each country.

Meta-regression analysis

We investigated the impact of various country characteristics on odds-ratio estimates through an inverse-weighted linear meta-regression analysis. The independent variable was the natural logarithm of the odds ratio. The explanatory factors included pre-defined country characteristics such as coverage of antiretroviral drugs use during PMTCT, HIV prevalence for females, sample size, sub-region and the calendar year of the survey. Other included factors were HDI, GDP and adult-literacy rates.

All the analyses were two-sided with $p < 0.05$ considered significant. Stata 14 (Stata Corp, College Station, TX, USA) software was used for analysis.[21]

Results

Description of included countries

This study included only 27 countries based on the availability of the required demographic and health surveys (DHS) HIV and immunisation data sets. The surveys were conducted between 2003 and 2016 in the included countries. The years 2013 and 2014 had the highest number of surveys totalling five each. The included countries, year of the survey, coverage of antiretroviral drugs used for PMTCT, HIV prevalence in females, gross domestic product (GDP) per capita, human development index (HDI), adult literacy rate and the sample sizes are shown in Table 1. A total number of 119,050 respondents were included in this study. A total of 4,187 out of 5,537 (75.6%) children of mothers living with HIV received DTP3, compared to 71,290 out of 113,513 (62.8%) children of HIV-uninfected mothers.

The percentage coverage of pregnant women who received antiretroviral drugs for PMTCT varied from 35% in Mali to 96% in Namibia. The HIV prevalence among females aged 15-49 years old ranged widely from 0.5% in Niger to 34.7% in Swaziland. Of the 27 countries, two are upper middle-income countries (Gabon and Namibia), eight are lower middle-income countries (Angola, Cameroon, Cote d'Ivoire, Ghana, Kenya, Senegal, Swaziland and Zambia) and the rest are low-income countries. The adult literacy rate ranged from 15.5% in Niger to 88.7% in Zimbabwe. The DTP3 coverage among the children of HIV-infected mothers varied between 24% in Angola and 96% in Rwanda while among the children of HIV-uninfected mothers it was 26% in Angola and 92% in Rwanda.

Table 1: Maternal HIV status, childhood DTP3 uptake, and other characteristics of 27 included countries

								Population sample size		
								Children of HIV-infected mothers		*Children of HIV-uninfected mothers*	
Country	**Year of survey**	**HIV prevalence**	**ARV coverage during PMTCT (%)**	**GDP per capita(US$)**	**HDI**	**Adult literacy rate**	**DTP3 uptake***	**Total number of children**	**DTP3 uptake***	**Total number of children**
Angola	2016	2.2	44	3110.8	0.533	66.0	21 (24)	88	1143 (30)	3757
Burkina Faso	2010	1.1	83	649.7	0.402	34.6	49 (83)	59	5397 (79)	6794
Burundi	2011	1.3	84	285.7	0.404	61.6	78 (88)	89	3035 (88)	3458
Cameroon	2011	5.1	74	1032.6	0.518	71.3	158 (73)	216	3019 (65)	4678
Chad	2015	1.6	63	664.3	0.396	22.3	27 (40)	67	1410 (26)	5337
Congo DR	2014	1	70	444.5	0.435	77.0	38 (42)	91	4238 (49)	8571
Cote d'Ivoire	2012	3.5	73	1526.2	0.474	43.9	67 (58)	115	1879 (57)	3270
Ethiopia	2003	1.3	69	706.8	0.448	39.0	71 (57)	124	3510 (35)	10094
Gabon	2012	5.3	76	7179.3	0.697	82.3	59 (35)	167	1309 (36)	3641
TheGambia	2013	2	69	473.2	0.452	42.0	40 (70)	57	2726 (77)	3528
Ghana	2014	2.1	56	1513.5	0.579	71.5	43 (77)	56	2129 (77)	2763
Guinea	2012	1.9	43	508.1	0.414	32.0	27 (52)	52	1440 (44)	3309
Kenya	2009	6.9	80	1455.4	0.555	78.7	147 (71)	206	1758 (73)	2412
Lesotho	2014	29.8	66	998.1	0.497	76.6	309 (80)	386	850 (79)	1078
Liberia	2013	2	70	455.4	0.427	42.9	22 (47)	47	1930 (57)	3373
Malawi	2016	11.2	84	300.8	0.476	62.1	199 (77)	258	2413 (83)	2893
Mali	2013	1.2	35	780.5	0.442	33.1	27 (60)	45	2707 (57)	4754
Namibia	2012	16.6	96	4140.5	0.64	88.3	17 (77)	22	3206 (60)	5365
Niger	2013	0.5	52	363.2	0.353	15.5	295 (79)	375	1412 (78)	1817
Rwanda	2015	3.8	82	702.8	0.498	68.3	131 (96)	137	3370 (92)	3659
Sao T&P	2009	n/a	n/a	1756.1	0.574	90.1	12 (63)	19	1471 (82)	1787
Senegal	2011	0.6	55	958.1	0.494	42.8	21 (66)	32	3048 (75)	4071
Sierra Leone	2013	2	87	496	0.42	32.4	44 (61)	72	3486 (70)	4952
Swaziland	2007	34.7	95	2775.2	0.541	83.1	676 (82)	822	1303 (85)	1542
Togo	2014	2.7	86	578.5	0.487	63.8	61 (87)	70	2496 (77)	3241
Zambia	2014	14.5	83	1178.4	0.579	83.0	1177 (85)	1378	8533 (80)	10673
Zimbabwe	2015	16.1	93	1008.6	0.516	88.7	371 (76)	487	2072 (77)	2696

ARV: anti-retroviral drugs; Congo DR- Congo Democratic Republic, DTP3: three doses of diphtheria-tetanus-pertussis containing vaccines, GDP: gross domestic product, HDI: human development index, n/a: not available, PMTCT: prevention of mother-to-child transmission, Sao T&P: Sao Tome and Principe

GDP - Low-income economies are defined as those with a GDP per capita of $1,025 or less; lower middle-income economies: $1,026 - $4,035; upper middle-income economies: $4,036 - $12,475; high-income economies: ≥ $12,476. HDI - low: <0.549; medium: 0.550 – 0.770. Percentage coverage of anti-retroviral drugs use during PMTCT – low: ≤ 50.0; ≥ 50.1. HIV prevalence – low: ≤ 10.0; ≥ 10.1. Adult literacy rate – low: ≤ 50.0; ≥ 50.1.

* The values for DTP3 uptake are absolute counts (percentage).

(Source: Demographic and Health Surveys, Joint United Nations Programme on HIV/AIDS, United Nations Development Programme)

Meta-analysis

The odds ratio (OR) and 95% confidence interval (CI) from the included countries and pooled result are shown in Figure 1. In most countries (n=20), there was no significant difference in the proportion of children of mothers living with HIV who received DTP3 and the children of HIV-uninfected mothers. In Sao Tome and Principe, and Malawi, children of mothers living with HIV were significantly less likely to receive DTP3 compared to the children of HIV-uninfected ones. However, in four countries, Cameroon, Chad, Ethiopia and Zambia, children of mothers living with HIV were significantly more likely to have received DTP3. Nonetheless, when the data from the 27 countries were pooled together using the DerSimonian-Laird method, there was no significant difference in DTP3 coverage between the two groups of women (OR = 1.05; 95% CI 0.91 - 1.22), with statistically significant heterogeneity (Chi^2 = 91.63 on 26 degree of freedom, P = 0.000, I^2 = 71.6%).

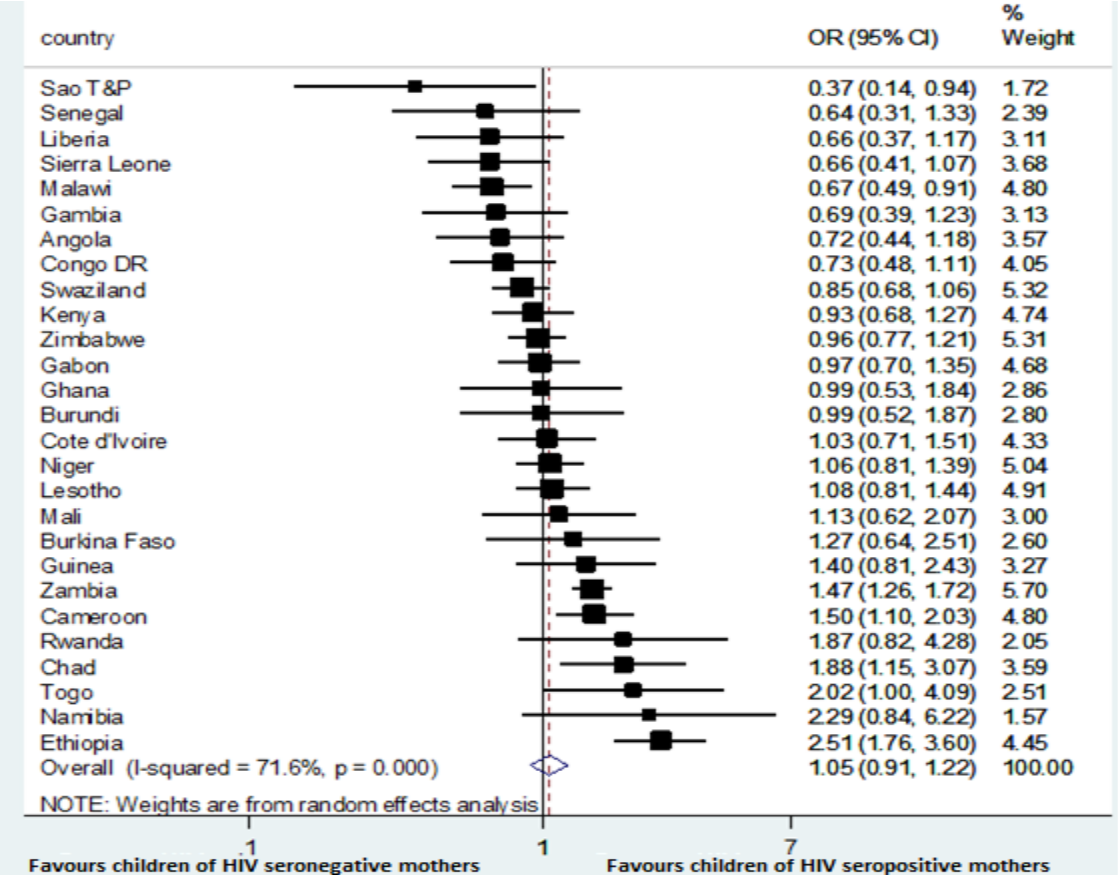

Figure 1: Forest plot showing the association between maternal HIV status and DTP3 coverage in 27 sub-Saharan Africa countries

Sub-group analyses

Sub-group analysis was conducted to access the effect of coverage of pregnant women who received antiretroviral drugs during PMTCT on the pooled estimates. The pooled estimates for countries with low and high coverage were calculated using the DerSimonian-Laird method. The pooled-effect estimates for the low-coverage countries was (OR = 1.04; 95% CI 0.90 - 1.21). The calculated pooled-effect estimates for the high coverage countries was (OR = 1.07; 95% CI 0.85 - 1.33) (Table 2). Sub-group analyses showed that differences between countries in terms of coverage for antiretroviral drugs, HIV prevalence, HDI, GDP, adult literacy rate, years of survey and sub-regions did not explain the heterogeneity of effect estimates on coverage for DTP3 vaccine among the sub-Saharan Africa children (Table 2).

Table 2: Subgroup analysis and the univariate meta-regression analysis result

Characteristics	No. of studies	Subgroup odds ratio	95% CI	I-squared	Univariate meta-regression	
					β	95% CI
Year of survey					0.97	0.92,1.02
2003-2010	5	1.1	0.9, 1.2	87.4*		
2011-2016	22	1.0	0.9, 1.2	64.8*		
HIV prevalence female					1.00	0.98, 1.02
Low	20	1.1	0.9, 1.3	65.4*		
High	6	1.0	0.8, 1.4	84.2*		
Pregnant women who receive anti-retroviral (%)					1.00	1.00, 1.01
Low	12	1.0	0.9, 1.2	17.9		
High	12	1.1	0.9, 1.3	76.7*		
Gross domestic product per capita (US$)					1.00	1.00, 1.00
Low	9	1.1	0.9, 1.3	72.3*		
Middle	18	1.0	0.8, 1.3	73.5*		
Human development index					0.83	0.10, 6.86
Low	21	1.0	0.9, 1.2	70.1*		
Medium	6	1.1	0.9, 1.2	72.7*		
Adult literacy rate					1.00	0.99, 1.01
Low	11	1.1	0.8, 1.5	73.4*		
High	16	1.0	0.9, 1.2	71.8*		
Regions					1.01	0.83, 1.23
Western Africa	13	1.0	0.8, 1.2	51.5*		
Central/Eastern Africa	7	1.2	0.9, 1.7	79.5*		
Southern Africa	7	1.0	0.8, 1.3	82.5*		
Size					1.00*	1.00, 1.00
Smaller studies	20	1.0	0.9, 1.1	44.3*		
Larger studies	7	1.4	1.0, 1.9	81.0*		

* $p < 0.05$

Sensitivity analyses

Figure 2 shows leave-one-country-out sensitivity analyses used to assess the stability of the meta-analysis. For the analyses, the overall estimate was calculated by removing one of the study countries each time. The changes in the confidence intervals with this exclusion remain within the 95% confidence interval for the overall estimate for all the included countries. The analyses show that no one country survey had an undue influence on the estimate of the association between maternal HIV status and DTP3 uptake. The outcome of these sensitivity analyses indicated the stability of the result.

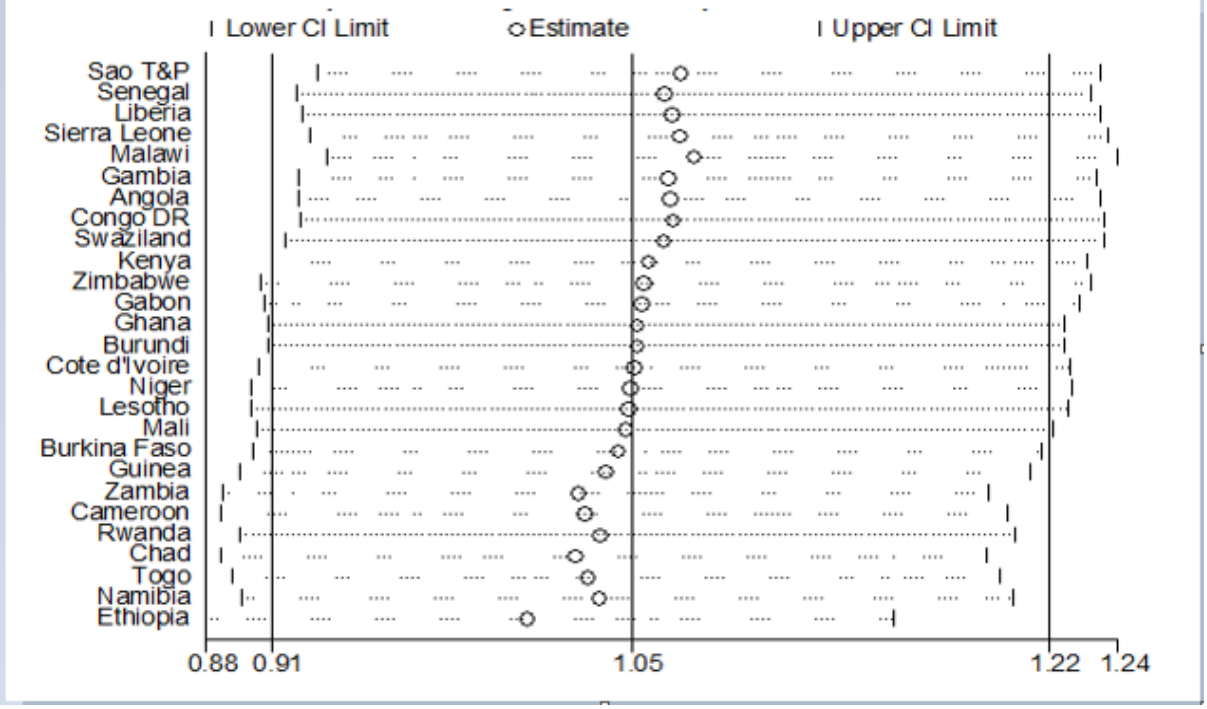

Figure 2: A plot showing the influence of each country on the overall pooled result using -leave-one-country-out' sensitivity analysis

Meta-regression analysis

Meta-regression analysis was performed to explore factors that might account for heterogeneity with respect to the country-level characteristics. We found that the coverage of antiretroviral drugs use during PMTCT was not significantly associated with the childhood DTP3 vaccination

coverage (p= 0.543). Likewise, other characteristics were not significantly associated with the DTP3 coverage except the sample size (p= 0.020) (Table 2).

Meta-regression plot of the natural logarithm of the odds ratio of DTP3 coverage regressed against the coverage of pregnant women who received antiretroviral drugs for PMTCT in each country (Figure 3). The circles represent a country and the size of each circle mirrors the effect of that country on the model. Although there was no significant relationship between the natural logarithm of the odds ratio of DTP3 coverage and the coverage of pregnant women who received antiretroviral drugs, however, the plot shows that the DTP3 coverage slightly increases as PMTCT coverage increases (β = 1.00, 95% Cl 0.99 - 1.01, p= 0.543) (Figure 3). Figure 4 also shows a bubble plot of DTP3 coverage slightly reducing as HIV prevalence increases.

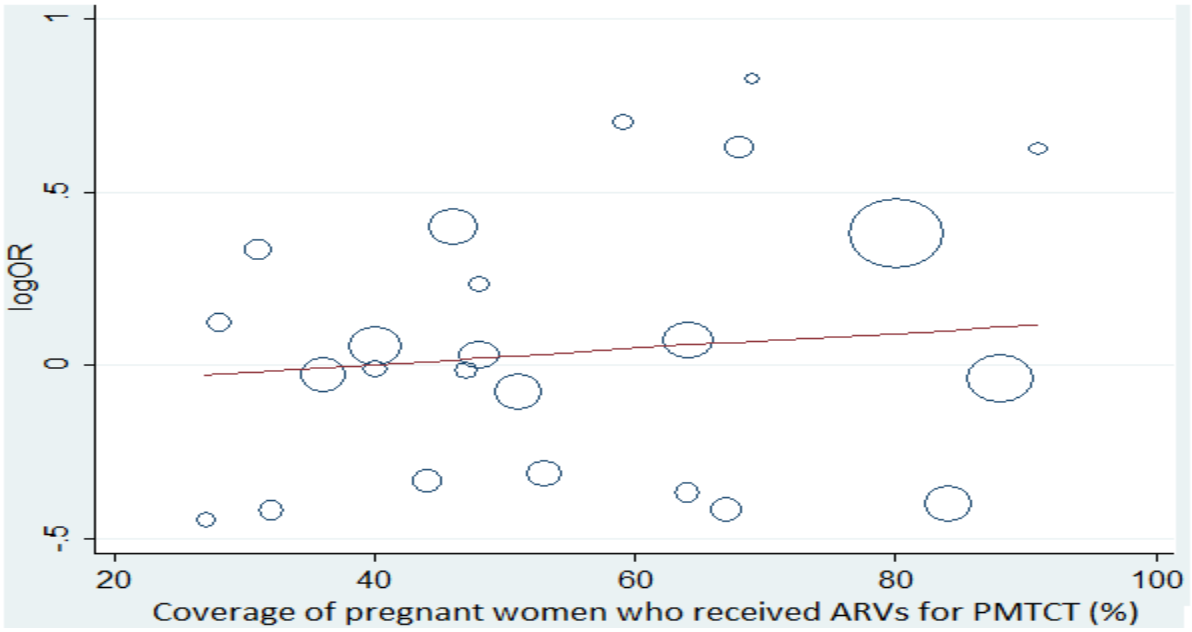

Figure 3: The association between the natural logarithm of the odds ratio for DTP3 coverage and coverage of women who received antiretroviral drugs for PMTCT in each included country

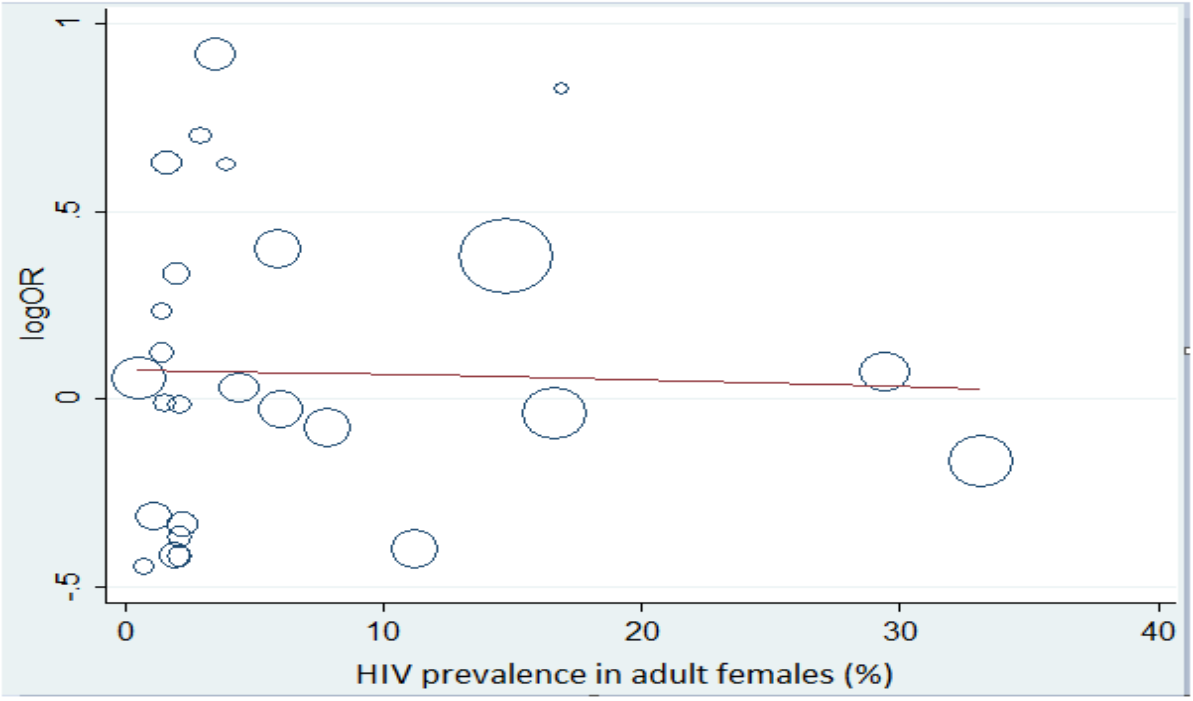

Figure 4: The association between the natural logarithm of the odds ratio for DTP3 coverage and adult female HIV prevalence in each included country

Discussion

The overall findings of the meta-analysis involving data from 27 sub-Saharan African countries showed that there is no significant difference in the DTP3 coverage among the infants of women living with HIV and those who are not HIV infected. The findings from this socio-ecological study show that there is low coverage of DTP3 vaccination among the HIV-exposed children, however, the DTP3 coverage among this group of children is higher than the HIV non-exposed children.

Studies by Eley and Seste et al. show that HIV-infected and HIV-exposed uninfected children are at risk for low immunisation coverage[22,23] while another study shows that the children of women living with HIV had more than a two-fold likelihood of being under-immunised than the children of mothers who are not HIV-infected.[24] A Nigerien study shows that children of HIV-infected women were less likely to receive second and third doses of DTP-containing vaccines while another study conducted in South Africa shows that HIV-exposed children are also less likely to complete the uptake of routine childhood vaccinations in comparison with the children of HIV-

uninfected women.[9,25] These African studies were conducted in rural and urban poor communities in Uganda, South Africa, Zambia and Niger with small sample sizes. Most of these studies were conducted prior to the era of comprehensive PMTCT programmes in Africa. This period witnessed unnecessary delays in implementing treatment policies, non-integration of services, Acquired Immunodeficiency Syndrome (AIDS) denialism views, lack of political will, widespread stigma and discrimination.[25,26] There were also issues of a weak health system and inadequate information about immunisation in most of the African countries at the time.[9,26,27]

It is worthy to note that the meta-regression analytic findings were not significant for most of the country characteristics apart from the sample size for individual country but the bubble plots show certain patterns that may explain some of the findings of the meta-analysis. DHS are large size cross-sectional surveys and likely to have a significant relationship with DTP3 coverage, however, the survey sample sizes do not have direct policy implication on the country DTP3 coverage. Meta-regression plot shows that DTP3 coverage slightly increases as the coverage of the pregnant women who received antiretroviral drugs for PMTCT increases (Figure 4). Likewise, the DTP3 coverage slightly reduces as the adult female HIV prevalence increases. Coverage of antiretroviral drugs for PMTCT and HIV prevalence for females are both important indicators which may contribute to the slight edge in DTP3 coverage recorded by the HIV-exposed children and explain the result of the meta-analysis.

The included DHS were mostly conducted post-2009 after the launch of the *Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive*. The Global Plan has the goal of reducing new HIV infections in children, decreasing the mother-to-child transmission rate of HIV and increasing the coverage of antiretroviral therapy in mothers and children.[27,28] The integration of PMTCT services into broad-based maternal, newborn, and child health services in many African countries in recent years has improved the quality and coverage of mother-child pair care support given to women living with HIV during the post-delivery and breastfeeding periods. There was a dramatic increase of about fivefold in the percentage of mothers or infants on antiretroviral therapy during breastfeeding from 2009 to 2013.[29] The mother-child pairs are now seen together and this gives easier access for early infant diagnosis, scheduled immunisation, timely initiation of antiretroviral treatment, cotrimoxazole prophylaxis, etc.[30] As shown by the findings of the meta-analysis and meta-regression, all these

interventions targeted at the women living with HIV and their children have not yielded significant differences in terms of vaccination coverage among this group. It is expected that level of DTP3 coverage in HIV-exposed children would be significantly higher especially with frequent routine clinic visits and scheduled immunisations. However, the reality on the ground shows that the mothers and caregivers of HIV-exposed children are faced with various challenges such as poor socio-economic status, stigma, discrimination especially at community level, poor awareness of immunisation benefits and negative attitudes of healthcare workers.[23,24,29,30] As is the case in the general population, low coverage of vaccination in HIV-exposed children could also be due to barriers that arise from the national healthcare system, healthcare providers and caregivers.[31]

As of 2016, Nigeria, Central African Republic, Niger, Chad, South Sudan, the Democratic Republic of the Congo, Mozambique, Madagascar, Uganda, Kenya, Somalia and Ethiopia were among the seriously challenged countries that needed Global Alliance for Vaccines and Immunisation (GAVI) support to meet their national immunisation targets.[32] The GVAP goal of achieving nationwide DTP3 vaccination coverage of at least 90% was not achieved in many of the included countries at the time of their surveys.[10] Only Rwanda achieved DTP3 uptake of more than 90% for the children of both HIV-infected and uninfected mothers. At the time of their surveys, Angola, Chad, the Democratic Republic of the Congo, Gabon, Guinea and Ethiopia recorded less than 50% coverage either for one or both of the two groups. DTP3 coverage, the proxy indicator of the performance of the national immunisation programmes, is relatively low in sub-Saharan Africa at 74% by the end of 2016.[33] The disparity in vaccination coverage among African countries could be as a result of conflict, economic decline or climate-related pressures.[32]

Efforts should be made to remove the barriers of vaccination uptake for the HIV-exposed and non-exposed children.[26,29] Implementing public-health interventions such as home visits to identify under-vaccinated or non-vaccinated children and regular immunisation outreach together with household incentives will help in improving the DTP3 coverage. Social determinants could help in transforming the DTP3 uptake irrespective of maternal HIV status by exploring the behavioural pattern of individuals and communities via well-structured interventions.[34]Interventions like the integration of immunisation activities into existing public healthcare programmes such as maternal and child health, antenatal care, PMTCT, antiretroviral treatment, HIV counselling and testing, and women-empowerment programmes will go a long way to improve DTP3 coverage.[35]

Improving DTP3 coverage among HIV-exposed and non-exposed children especially those living in the rural and urban poor areas requires a multidimensional collaboration.[30,31] This entails vaccinating eligible children at every opportunity, address community stigma, mapping out low-coverage areas, community mobilisation and referral for immunisation.[30,36]

Limitations and strengths

Conducting this meta-analysis permits the synthesis of findings and allows comparison across numerous studies.[37] DHS being a nationally represented survey has many advantages over primary studies that are limited to geographical locations. This study has several limitations such as the non-inclusion of data from South Africa and Nigeria that are the two countries with the largest population of women living with HIV and HIV-infected children. The two countries were excluded due to the lack of a DHS HIV data set. As an ecological study with cross-sectional design and likeness of ecological fallacy, care must be taken in attributing the causal relationships detected in this research.

Conclusions

In conclusion, the findings from this study will be beneficial to the public healthcare system in terms of improving the vaccination coverage of HIV-exposed children in sub-Saharan Africa. The study indicates that there is no significant difference in the DTP3 coverage among infants concerning maternal HIV status in sub-Saharan Africa, however, there is a significant variation in terms of the estimates among the sub-Saharan African countries. The DTP3 coverage for both HIV-exposed children and non-exposed children is still below the required target. Improved PMTCT and maternal and child health services across the board might have contributed to the better uptake of DTP3 vaccination among the HIV-exposed children than the non-exposed children. There is also the need to address various barriers impeding successful uptake of vaccination among HIV-exposed and non-exposed children. Collaboration is required to improve vaccination coverage of HIV-exposed children and to reduce the risk of contracting vaccine-preventable diseases.

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome

ARV: Antiretroviral drugs

CI: Confidence intervals

DHS: Demographic and health survey

DTP: Diphtheria-tetanus-pertussis

GAVI: Global Alliance for Vaccines and Immunisation

GDP: Gross domestic product

GVAP: Global Vaccine Action Plan

HDI: Human Development Index

HIV: Human Immunodeficiency Virus

OR: Odds ratio

PMTCT: Prevention of mother-to-child transmission

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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Contributions

OOA and OAU conceived the study. OOA did the data analysis, interpreted the results and wrote the initial manuscript. OAU assisted with the data analysis. OAU and CSW reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

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CHAPTER 5: Non-uptake of childhood vaccination among the children of HIV-infected mothers in sub-Saharan Africa: A multilevel analysis

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Abstract

The aim of this study was to develop and test models for non–uptake of three doses of diphtheria-tetanus-pertussis containing vaccines (DTP3) among children of women living with HIV in sub-Saharan Africa. The study used demographic and health survey data from 27 sub-Saharan African countries that have the required HIV and immunisation data sets. Multivariable logistic regression models were used to assess the relationship between individual and contextual factors associated with non-uptake of DTP3 among the children. At the individual level, the odds of non-uptake of DTP3 decreased with formal education, increasing age and access to media. The full model shows that the odds of non-uptake of DTP3 are increased among unemployed women, those living in communities with high illiteracy rates and in countries with low adult literacy levels. For a child who moves to another country or community with a higher probability of DTP3 non-uptake, the median increase for the odds of DTP3 non-uptake would be 2.24% and 1.22% respectively for country and community. This study shows that individual and contextual factors contributed significantly to non-uptake of DTP3 among the children of women living with HIV. Interventions should be focused on women living with HIV who are young mothers, unemployed women, those without formal education, individuals living in communities with high illiteracy rates and in countries with low adult literacy rates. The use of mass-media tools and the creation of more employment opportunities for HIV-infected women could improve vaccination coverage amongst their children.

***Keywords*:** diphtheria-tetanus-pertussis; HIV; vaccine-preventable diseases; sub-Saharan Africa; demographic and health survey

Introduction

Research studies have shown that routine vaccination coverage is inadequate in several African countries and unable to meet national targets for Global Vaccine Action Plan (GVAP).[1–3] Sub-Saharan Africa, which has high HIV prevalence, needs adequate vaccination coverage especially among the HIV-infected and HIV-exposed children because they are highly susceptible to severe forms of some vaccine-preventable diseases with a resultant increased risk of mortality.[4,5] The children of HIV-infected mothers are at greater risk of mortality than non-exposed children because HIV-infected mothers may not take their children for vaccination as scheduled due to generalised weakness and non-availability of transport fees to get to the healthcare facilities.[6,7] Vaccination of both HIV-infected and uninfected children also plays a critical role in achieving Millennium Development Goal 4 which is targeted at reducing deaths in children under-five years of age.[8] Sustainable Development Goal 3.8 is also connected to vaccination strategies especially the achievement of Universal Health Coverage via vaccines for all age groups.[9]

Studies show that children born to HIV-infected mothers were less likely to receive all the basic vaccination according to schedule through the avoidance of community health facilities owing to stigma and discrimination.[6,7,10] The association between maternal HIV status and childhood vaccination is of public-health significance in countries with high HIV prevalence. However, there is uncertainty and limited information on factors that influence the association between maternal HIV status and childhood vaccination coverage in sub-Saharan Africa.[10]

It has been established that there is an association between maternal education and vaccine uptake, however, this varies across different regions and settings across the world.[11] Studies have also shown that the odds of childhood vaccination are greater in children whose mothers had secondary or higher education.[11,12] Poor socio-economic status and non-empowerment of women are important factors related to poor uptake of childhood vaccination.[12] Immunisation coverage is low in urban poor and deprived neighbourhoods. These neighbourhoods usually also have poor mother and child healthcare services, maternal illiteracy, poor household socio-economic status and gender inequality.[13]

The per capita gross domestic product (GDP) is a key factor in the usage of vaccines in low-income countries that have high mortality rates due to vaccine-preventable diseases. It is expected that good vaccine uptake in these countries will be cost-effective on the long run and this depends

largely on the cost of the vaccination programme relative to GDP,[14] Vaccination plays an important role in economic growth. It has an impact on a country's healthcare with resultant reduction in mortality and morbidity, thereby contributing to the GDP.[15]

Efforts such as WHO-UNICEF Global Immunization Vision and Strategy, GAVI Alliance Strategy, Global Vaccine Action Plan (GVAP) and Expanded Programme on Immunisation (EPI) were put in place to improve vaccination coverage sub-Saharan Africa and other parts of the world. GVAP Global Vaccine is a framework for achieving the delivery of universal access to immunisation.[3] There is a dearth of information concerning interventions or programmes targeted at improving vaccination coverage specifically for HIV-infected and HIV-exposed uninfected children in Africa. Vaccination programmes target all children irrespective of their HIV status or that of their mothers although there are some specific recommendations for HIV-infected children.[16] A multilevel study is specifically needed to evaluate the independent contributions of individual, community, and country-level factors to non-vaccination among the children of HIV-infected women in sub-Saharan African countries.

The aim of this study was to develop and test models for non-uptake of the third dose of diphtheria-tetanus-pertussis containing vaccines (DTP3) among the children of HIV-infected mothers. DTP-containing vaccines provide immunity against diphtheria, tetanus and pertussis. These three infectious diseases lead to significant morbidity and mortality in children especially in countries with poor vaccination coverage. The World Health Organization (WHO) recommends the uptake of three doses of primary vaccination of DTP-containing vaccines followed by three booster doses.[16]

Methods

Study design

This study consisted of secondary data analyses of the cross-sectional population-based demographic health surveys (DHS) from 27 sub-Saharan African countries namely: Angola, Burkina Faso, Burundi, Cameroon, Chad, the Democratic Republic of the Congo, Cote d'Ivoire, Ethiopia, Gabon, The Gambia, Ghana, Guinea, Kenya, Lesotho, Liberia, Malawi, Mali, Namibia, Niger, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, Swaziland, Togo, Zambia and

Zimbabwe. Only 27 African countries with available DHS HIV and vaccination data sets were included in this study.

Sampling technique

The DHS were conducted in different African countries with focus on health, demographic, socio-economic and environmental indicators from a representative sample of women and men in households across the included countries. The DHS sampling frame is made up of enumeration areas (clusters) established in each of these countries. A two-stage probabilistic sampling method was also used for survey cluster selection.

Data collection

Data were collected by the use of standardised questionnaires administered to various respondents by trained interviewers. The implementation of the surveys was spearheaded in each country by the National Ministry/Department of Health or other responsible agencies with technical assistance from MEASURE DHS, ICF International, Calverton, Maryland, USA. Development partners such as the United States Agency for International Development (USAID), the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), etc. provided some of the funds for the project. This study included countries that collected data on uptake of the three doses of diphtheria-tetanus-pertussis containing vaccines (DTP3) as well as HIV voluntary counselling and testing in the participating women up to November 2017.

The participating women were aged between 15 and 49 years and tested for HIV during the household survey with consent. Field staff with the required skills and experience were recruited to work as interviewers and were trained according to the DHS training procedures. The interviewers identified members of the household eligible for biomarker collection. The interviewers explained the purpose of the HIV testing to eligible respondents and assured them of confidentiality prior to the test. HIV data were collected from eligible, consenting women after the completion of their individual interview. The interviewers collected finger-prick dried blood-spot samples for laboratory HIV testing. The DHS data collection and analysis used a programme protocol specifically designed to include the outcomes like laboratory HIV test and other data attributed to each participating respondent. The women were asked detailed information on their

children's vaccination history and vaccination cards were also checked to verify the mother's claims.

Ethical consideration

The data used for this study were obtained from an existing DHS database. All the identifier information was removed so that the data cannot be traced to a particular individual. Each DHS was approved by the respective National Health Research Ethics Committees of the participating countries and Institutional Review Boards of the ICF International, Calverton and the Centers for Disease Control and Prevention, Atlanta, USA.

Outcome variable

The outcome is defined as a binary variable with the value of '1' if there was no uptake of DTP3 and '0' if there was an uptake among children aged 12-23 months at any time before the survey as reported on their vaccination cards or by their mothers during interviews. The analysis is limited to the children of HIV-infected mothers.

Determinant variables

Individual-level factors

The study included the following individual-level factors in the models: the child's gender (male or female), the age of the mother in completed years (15 to 24, 25 to 34, 35 and above), educational status of the mother (no basic education, primary, secondary or higher), employment status of the mother (whether unemployed or employed), and wealth index (poorer, middle or richer).

Community-level factors

The following community-level factors were included in the model: neighbourhood poverty rate (percentage of households that are below 20% of the wealth index), illiteracy rate (the percentage of women without formal education within the community), unemployment rate (percentage of women unemployed in the community) and place of residence (either urban or rural). The rates were classified as low or high.

Country-level factors

The following country-level factors were included in the model: gross domestic product per capita, adult literacy rate and health expenditure per capita. These data were obtained from World Bank

Data.[17] The country-level variables were also categorised into either low or high in order to assess nonlinear effects and for easy interpretation of results for policy decision making.

Statistical analyses

The statistical analyses were done with STATA 14.0 (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).[18] The distribution of respondents was expressed as percentages. Pearson Chi-Square was used to assess the relationship between DTP3 uptake and various variables. Multivariable logistic regression models were used to analyse the association between individual and contextual factors associated with non-uptake of the third dose of DTP3 vaccines among the children of women living with HIV. A three-level model for binary response reporting non-uptake of DTP3 vaccination among the children of women living with HIV (level 1), in a particular community (level 2) and living in a particular country (level 3). Figure 1 shows the conceptual framework for the models at different levels. This framework will guide towards understanding the objectives of this study.

The study used five models namely:

First model: empty null model, an unconditional model without any explanatory variables.

Second model: for only individual-level factors.

Third model: for only community-level factors.

Fourth model: for only country-level factors.

Fifth model (Full model): that controlled for individual-, community- and country-level factors simultaneously.

The fixed-effects (measure of association) results were reported as odds ratios (ORs) with their corresponding 95% credible intervals (CrIs). The random-effects (measures of variation) results such as variance, intra-cluster correlation (ICC), and median odds ratio (MOR) were also reported. The MLwinN software, version 3.01 was used for model fit analyses[19,20] while Wald test[21] was used to calculate the statistical significance of covariates. The significance tests were two-tailed and significance defined at the 5% α- level.

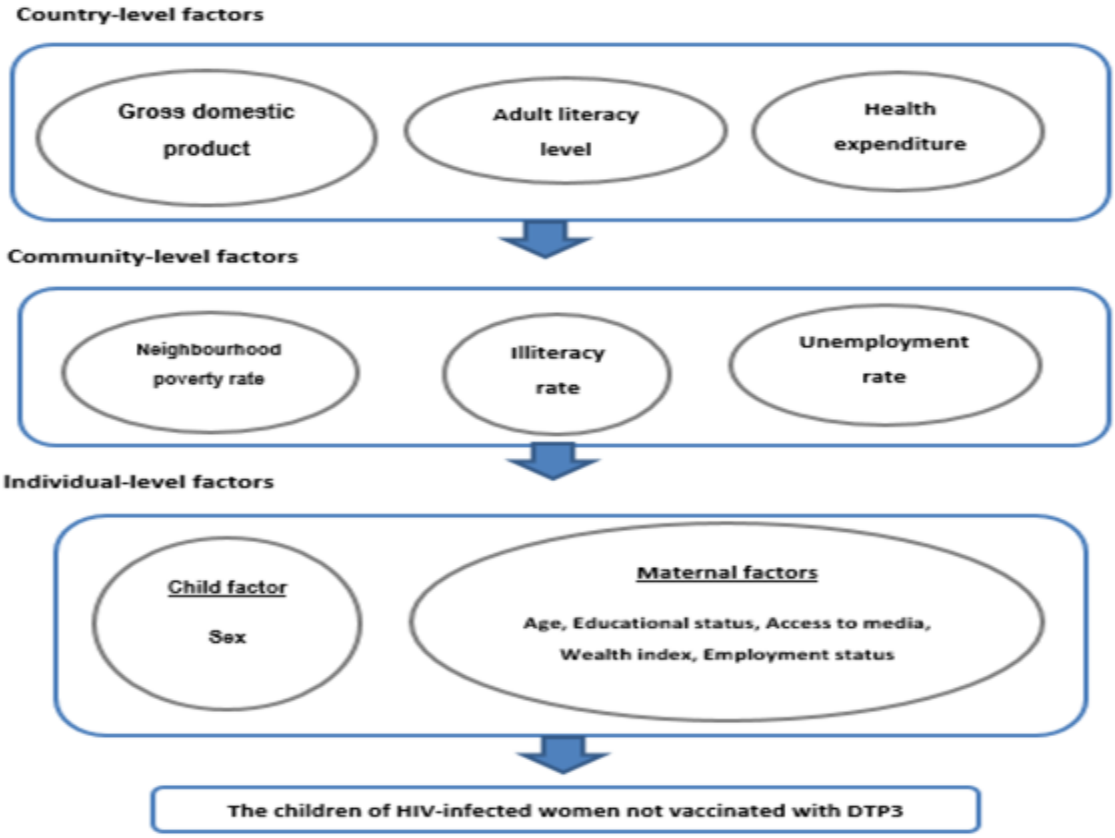

Figure 1: Conceptual framework showing the factors determining non-uptake of DTP3-containing vaccines by the children of HIV-infected mothers

Results

Sample characteristics

Table 1 shows the summary of individual, community and country characteristics, and DTP3 coverage among the children of HIV-infected mothers. A total of 5,537 children aged 12-23 months, within 2841 communities and from 27 countries in sub-Saharan Africa were involved in this study. About one-fourth of the children of HIV-infected mothers did not receive DTP3 prior to the survey. The numbers of male and female children were fairly and evenly distributed. Table 1 shows that there was an association between DTP3 uptake and variables such as age, level of education, employment status, access to media, wealth index and illiteracy rate. The table also shows that DTP3 vaccination is not significantly associated with years of survey. Country-level characteristics are shown in Table 2. The surveys were conducted between 2003 and 2016 in the included countries with the years 2013 and 2014 having five surveys each.

Measures of associations (fixed effects)

Table 3 shows the results of different models. At the individual level, the odds of non-uptake of DTP3 decreased with formal education, increasing age and access to media. At community level, the odds of DTP3 non-uptake increased with being resident in communities with high illiteracy rates. The full model shows that the odds of the children of women living with HIV not receiving DTP3 vaccination increased with being unemployed, such that the children of unemployed women were 17% more likely not to take DTP3 (OR = 1.171, 95% CrI 1.012 to1.372). The odds of not completing the vaccination schedule decreased with older maternal age, such that children of women aged 35-49 years were 29% less likely to miss DTP3 compared to children of women aged 15-24 years old (OR = 0.711, 95% CrI 0.584 to 0.856). Other factors that decreased the odds of not completing the vaccination schedule were formal education and access to media (Table 3).

There was also a significant association between non-uptake of DTP3 and countries with low adult literacy rate (Table 3). Countries such as Burkina Faso, Chad, Cote d'Ivoire, Ethiopia, The Gambia, Guinea, Liberia, Mali, Niger, Senegal and Sierra Leone which are mainly West African countries are the ones with low adult literacy rate (Table 2). Women living with HIV in these countries are less likely to have their children vaccinated with DTP3.

Measures of variations (random effects)

In model 1 (unconditional model), there was a significant variation in the odds of non-vaccination with DTP3 of the children of HIV-infected mothers across the countries (σ^2 = 0.852, 95% CrI 0.457 to 1.503) and across the communities (σ^2 = 0.002, 95% CrI 0.000- 0.004) (as shown in Table 3). The intra-country and intra-community correlation coefficients show that 20.57% and 20.61% of the variance in odds of non-uptake of DTP3 are linked to country- and community-level factors respectively. The variance in odds of not being vaccinated with DTP3 was also attributable to the country- and community-level factors respectively. From the full model (Model 5), it is assumed that a child who moved to another country or community with a higher probability of DTP3 non-uptake, the median increase in the odds of DTP3 non-uptake would be 2.24% and 1.22% respectively.

Table 1: Summary of characteristics at different levels and DTP3 uptake among children of HIV-infected mothers

			DTP3 uptake		
Variables	**Sample size**	**Percentage**	**No***	**Yes***	**p-value**
DTP3 non-uptake	1,350	24.4			
DTP3 uptake	4,187	75.6			
Years of survey					
2003-2010	1,230	22.2	275 (20.4)	955 (22.8)	0.061
2010-2011	4,307	77.8	1,075 (79.6)	3,232 (77.2)	
Individual-level factors					
Gender					
Female	2,734	49.4	673 (49.8)	2,061 (49.2)	0.688
Male	2,803	50.6	677 (50.2)	2,126 (50.8)	
Age (in years)					
15-24	1,352	24.4	355 (26.3)	997 (23.8)	0.003
25-34	2,828	51.1	710 (52.6)	2,118 (50.6)	
35-49	1,357	24.5	285 (21.1)	1,072 (24.5)	
Education					
No education	855	15.4	315 (23.3)	540 (12.9)	0.000
Primary	2,363	42.7	541 (40.1)	1,822 (43.5)	
Secondary+	2,319	41.9	494 (36.6)	1,825 (43.6)	
Employment status					
Unemployed	2,093	37.8	552 (40.9)	1,541 (36.8)	0.007
Employed	3,444	62.2	798 (59.1)	2,646 (63.2)	
Wealth index					
Poorer	1,514	27.3	397 (29.4)	1,117 (26.7)	0.000
Middle	1,694	30.6	447 (33.1)	1,247 (29.8)	
Richer	2,329	42.1	492 (37.5)	1,823 (43.5)	
Access to media					
Nil	1,302	23.5	398 (29.5)	904 (21.6)	0.000
Access to 1 outlet	1,697	30.7	418 (31.0)	1,279 (30.6)	
Access to 2 outlets	1,578	28.5	347 (25.7)	1,231 (29.4)	
Access to all outlets	960	17.3	187 (13.9)	773 (18.5)	
Community-level factors					
Place of residence					
Urban	2,477	44.7	603 (44.7)	1,874 (44.8)	0.953
Rural	3,060	55.3	747 (55.3)	2,313 (55.2)	
Poverty rate					
Low	3,421	61.8	805 (59.6)	2,616 (62.5)	0.061
High	2,116	38.2	545 (40.4)	1,571 (37.5)	
Unemployment rate					
Low	2,816	50.9	675 (50.0)	2,141 (51.1)	0.468

High	2,721	49.1	675 (50.0)	2,046 (48.9)	
Illiteracy rate					
Low	3,609	65.2	804 (59.6)	2,805 (67.0)	0.000
High	1,928	34.8	546 (40.4)	1,382 (33.0)	

* The values for DTP3 uptake are absolute counts (percentage).

Table 2: Country-level characteristics of the 27 included countries

Country	Year of survey	GDP per capita (US$)	Adult literacy rate	Health expenditure per capita (US $)
Angola	2016	3110.8	66.0	179.4
Burkina Faso	2010	649.7	34.6	35.2
Burundi	2011	285.7	61.6	21.6
Cameroon	2011	1032.6	71.3	58.7
Chad	2015	664.3	22.3	37.1
Congo DR	2014	444.5	77.0	19.1
Cote d'Ivoire	2012	1526.2	43.9	88.4
Ethiopia	2003	706.8	39.0	26.6
Gabon	2012	7179.3	82.3	321.3
The Gambia	2013	473.2	42.0	30.7
Ghana	2014	1513.5	71.5	57.9
Guinea	2012	508.1	32.0	37.3
Kenya	2009	1455.4	78.7	77.7
Lesotho	2014	998.1	76.6	105.1
Liberia	2013	455.4	42.9	46.3
Malawi	2016	300.8	62.1	29
Mali	2013	780.5	33.1	47.8
Namibia	2012	4140.5	88.3	499
Niger	2013	363.2	15.5	24.4
Rwanda	2015	702.8	68.3	52.5
Sao T&P	2009	1756.1	90.1	165.6
Senegal	2011	958.1	42.8	49.5
Sierra Leone	2013	496	32.4	85.9
Swaziland	2007	2775.2	83.1	247.9
Togo	2014	578.5	63.8	33.9
Zambia	2014	1178.4	83.0	85.9
Zimbabwe	2015	1008.6	88.7	57.7

Congo DR - Congo Democratic Republic, GDP: gross domestic product, Sao T&P: Sao Tome and Principe; US$: United States Dollars
GDP - Low-income economies are defined as those with a GDP per capita of $1,025 or less; lower middle-income economies: $1,026 - $4,035; upper middle-income economies: $4,036 - $12,475; Adult literacy rate – low: ≤ 50.0; high: ≥ 50.1; Health expenditure – low: ≤ 100.0; Average: ≥ 100.1.
(Source: World Bank, United Nations Development Programme)

Table 3: Factors associated with non-uptake of DTP3-containing vaccines by children of HIV-infected women identified by multilevel multivariate logistic-regression models

	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 5[e]
	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)
Fixed-effect					
Individual-effect factors					
Male (vs female)		0.961 (0.844-1.095)			0.959 (0.838-1.091)
Age (in completed years)					
15-24		1 (reference)			1 (reference)
25-34		0.932 (0.793-1.089)			0.937 (0.793-1.087)
35-49		0.699 (0.574-0.844)*			0.706 (0.575-0.849)*
Wealth index					
Poorer		1 (reference)			1 (reference)
Middle		1.094 (0.907-1.307)			1.055 (0.860-1.286)
Richer		0.880 (0.718-1.076)			0.830 (0.639-1.069)
Education					
No education		1 (reference)			1 (reference)
Primary		0.700 (0.564- 0.860)*			0.768 (0.612-0.957)*
Secondary+		0.656 (0.519-0.831)*			0.719 (0.566-0.927)*
Not employment		1.149 (0.990-1.327)			1.172 (1.001-1.365)*
Access to media		0.899 (0.828- 0.974)*			0.893 (0.826-0.962)*
Community-level factors					
Rural (vs urban)			1.085 (0.903-1.288)		0.965 (0.795-1.182)
High (vs low) poverty rate			0.999 (0.943-1.056)		0.965 (0.899-1.032)
High (vs low) unemployment rate			0.992 (0.950-1.041)		0.980 (0.924-1.042)
High (vs low) illiteracy rate			1.099 (1.050-1.152)*		1.052 (0.995-1.110)
Country-level factors					
Middle (vs low) GDP				1.496 (0.531-2.920)	1.561 (0.585-3.046)
High (vs low) Adult literacy rate				0.482 (0.207-1.139)	0.489 (0.230-0.936)*
Average (vs low) Health expenditure				2.289 (0.665-6.258)	2.235 (0.570 -5.480)
Random effects					
Country-level					
Variance (95 CrI)	0.852 (0.457-1.503)	0.785 (0.415-1.420)	0.826 (0.439-1.478)	0.732 (0.371- 1.371)	0.723 (0.364-1.347)
ICC (%)	20.57	19.26	20.06	18.18	17.83
MOR ((%, 95% CrI)	2.40	2.32	2.37	2.25	2.24
Explained variation (%)	Reference	7.90	3.10	14.20	15.20
Community-level					
Variance (95 CrI)	0.002 (0.000- 0.004)	0.002 (0.001 to 0.003)	0.003 (0.001-0.005)	0.003 (0.001- 0.005)	0.042 (0.014-0.072)
ICC (%)	20.61	19.30	20.12	18.24	18.87
MOR ((%, 95% CrI)	1.04	1.04	1.05	1.05	1.22
Explained variation (%)	Reference	-10.50	-68.70	-70.40	-2679.90
Model fit statistics					
DIC	5641	5593	5629	5640	5584

DIC - Deviance Information Criterion; ICC – intra-cluster correlation; MOR – median odds ratio; OR- odds ratio; CrI – credible interval.
[a]Model 1 is a null model, baseline model without any determinant variable. [b]Model 2 is additionally adjusted for individual-level factors.
[c]Model 3 is additionally adjusted for community-level factors. [d]Model 4 is additionally adjusted for country-level factors.
[e]Model 5 is additionally adjusted for individual-, community-, and country-level factors. *: $p < 0.05$

Discussion

Main findings

This study demonstrated that the individual, community and country contexts in which the children of HIV-infected mothers live are closely associated with non-uptake of DTP3. These factors are significant in explaining the variations in non-uptake of DTP3 in the children of HIV-infected mothers in the selected sub-Saharan African countries. Non-uptake of DTP3 is less likely in children of women living with HIV who were employed, within the age group 35-49 years, educated and with access to media. It could then be extrapolated that the children of HIV-infected women who were unemployed, younger, uneducated, and without access to media are more likely to miss out on DTP3 uptake. DTP3 non-uptake is also associated with the children of HIV-infected women living in communities with high illiteracy levels and in countries with low adult literacy rates. Some of these findings conform to an earlier South African study.[22]

These findings show that the unemployed status of HIV-infected mothers contributes to their children being incompletely vaccinated. Unemployment at the individual level was not significant for non-vaccination but with other factors interplaying at the community and country levels, unemployment became a significant factor. The inability of the unemployed and poorer mothers to source funds for transport to health centres for scheduled vaccinations may be a vital reason for the non-uptake of the vaccines.[23,24] Unemployment leads to poverty, and studies have shown that the more the poverty level of a household, the more likely it is that its children would be incompletely vaccinated.[25] Lack of basic resources leads to poor health-seeking behaviour and deprivation of required immunisation, and subsequently being exposed to vaccine-preventable diseases.[25]

The low likelihood of the younger HIV-infected mother, possibly having her first child, to take her child for vaccination may be as the result of lack of information concerning the importance of immunisation. Older women, having cared for many children, are likely to know the importance of immunisation.[25,26] This study shows that education plays a major role in improving vaccination coverage. The probability of a child of an HIV-infected mother not taking DTP3 is reduced in women with any form of formal education compared to their uneducated counterparts. This gives

credence to similar studies on immunisation in the general population in some African countries.[23-25,27] Many of the countries that have low adult literacy rates are also among the countries that are in dire need of support by GAVI in order to meet their individual national immunisation targets.[28] All of this shows that literacy level has a significant impact on vaccination coverage and national immunisation programmes. Furthermore, our findings demonstrate the clustering effects of non-uptake of vaccinations at community and country levels. This implies that HIV-exposed children from the same communities were inclined to have similar vaccination status and are subjected to similar contextual characteristics within the communities.[29]

Policy implications

There is a need for an evidence-based methodology to investigate why various immunisation programmes are not reaching the expected targets. Understanding the factors responsible for successful implementation of immunisation programmes among HIV-exposed children in sub-Saharan Africa is crucial for policy making. Appropriate approaches are needed to tackle various identified gaps in immunisation programmes specifically among HIV-exposed children. Evidence-based approaches are also needed to manage scarce resources needed for health interventions and disease prevention.[30,31] The findings from this multilevel analysis show that mothers who were educated, older, employed and have access to media were less likely to have had their children vaccinated with DTP3. These findings also imply that lack of education, age, unemployment and, lack of access to media are significant contributory factors to the problem of non-uptake of life-saving vaccines among the children of women living with of HIV in sub-Saharan Africa. Non-uptake of DTP3 was also found to cluster within communities, thus escalating the risk of vaccine-preventable diseases among HIV-exposed and infected children.

Public-health interventions should be designed specifically for women living with HIV who are young mothers, unemployed and without formal education. The remedial interventions should also focus on HIV-infected women who are resident in communities with high illiteracy rates in Africa. Our findings show that access to media reduces non-uptake, therefore, intervention such as the use of mass media should be in place in the areas with need. The use of multimedia interventions has been proven to be effective and useful for childhood immunisation programmes among sub-Saharan African countries and could be adapted for HIV-exposed and infected children.[32] The use

of interactive clinician-delivered communication tools have been found to improve mothers' knowledge and understanding of good health.[33]

Immunisation activities should be promoted among HIV-infected parents right from the time of the antenatal care and also integrated as part of broader prevention of mother-to-child HIV transmission programme.[34] Interventions that provide parents, caregivers and other community members with information on the benefits of immunisation may improve childhood vaccination coverage in communities and countries.[35,36] All these interventions should also be in place for people who are not HIV-infected as well. There should be renewed efforts to educate the girl child in Africa as it has been proven that being educated improves vaccination uptake. Special attention is needed in countries with high rates of illiteracy since this impacts negatively on vaccine uptake. Factors like wealth index, residency, gender and GDP were not associated with DTP3 non-uptake and therefore warrant lesser attention in terms of interventions and policy changes.

Limitations and strengths of this study

DHS are considered as very reliable source of population-health data in low- and middle-Income countries. DHS are large, nationally representative surveys involving every section/region of the included countries and with high response rates. The surveys are, however, subject to social desirability and recall bias. As they are cross-sectional studies, the data cannot be used to assess causal relationships between the variables. The included surveys were conducted at different times across the countries within a 13-year timeframe, however, Table 1 shows that this did not impact negatively on the study findings.

Conclusion

This study shows that individual and contextual factors contributed significantly to non-uptake of DTP3 among the children of HIV-infected women across sub-Saharan Africa. Policy making regarding childhood vaccination and public-health interventions targeted at improving childhood immunisation uptake among HIV-exposed and HIV-infected children should incorporate all the contributory factors during the planning, designing and implementation. The interventions should be developed with focus on young mothers, unemployed women, those without formal education and those living in communities with high illiteracy rates. Particular attention should also be given

to women living with HIV who are residents of African countries with low adult literacy rates. The use of mass-media tools will help improve the mothers' knowledge and understanding of immunisation good health. Efforts should also be made to create more employment opportunities for unemployed women living with HIV.

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome

CrIs: Credible intervals

DHS: Demographic and Health Survey

DTP: Diphtheria-tetanus-pertussis

GAVI: Global Alliance for Vaccines and Immunisation

GDP: Gross domestic product

GVAP: Global Vaccine Action Plan

HIV: Human Immunodeficiency Virus

OR: Odds ratios

US$: United States Dollar

WHO: World Health Organization

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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Contributions

OOA and OAU conceived the study. OOA did the data analysis, interpreted the results and wrote the initial manuscript. OAU assisted with the data analysis. OAU and CSW reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

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CHAPTER 6: Morbidity benefit conferred by childhood immunisation in relation to maternal HIV status: a meta-analysis of demographic and health surveys

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Abstract

The study determined the prevalence of acute respiratory infections and diarrhoea among sub-Saharan African children. It also examined if there was any significant morbidity benefit conferred by three doses of diphtheria-tetanus-pertussis containing vaccines (DTP3) with respect to maternal HIV status**.** Data were obtained from the Demographic and Health Survey (DHS) program, United Nations Development Programs, the World Bank and Joint United Nations Programme on HIV/AIDS. Pooled odds ratio (OR) and 95% confidence intervals (CI) were calculated for the countries. Tests of heterogeneity, sensitivity analyses and meta-regression were also conducted. The prevalence of acute respiratory infections and diarrhoea were similar between the children that were vaccinated and those who were not vaccinated with DTP3. The pooled result shows that children who did not receive DTP3 were more likely to have symptoms of acute respiratory infections than children who had DTP3 (OR 1.09, 95% CI 1.02 to 1.17); with low heterogeneity across the countries. The combined result for diarrhoea shows that children who did not receive DTP3 were less likely to have episodes of diarrhoea than children who received DTP3 (OR 0.83, 95% CI 0.74 to 0.92); with substantial heterogeneity across the countries. There was no difference between the estimates of DTP3 vaccinated and unvaccinated children of HIV-infected mothers with respect to symptoms of acute respiratory infections or episodes of diarrhoea. Tackling various causes and risk factors for respiratory-tract infections and diarrhoeal diseases should be a priority for various stakeholders in sub-Saharan Africa.

Keywords**:** Acute respiratory infections; diarrhoea; HIV; sub-Saharan Africa; demographic and health surveys

Background

There were 5.9 million deaths in children under-five worldwide in 2015 with half caused by vaccine-preventable diseases.[1,2] Medical conditions such as pneumonia and diarrhoea were leading causes of death among children under-five in sub-Saharan Africa.[1] Acute respiratory infections (such as pneumonia) and diarrhoeal diseases place a considerable burden on health services, including multiple hospital visits and admissions.[3] Human immunodeficiency virus (HIV) infection is a leading cause of disease burden and years of life lost in sub-Saharan Africa.[4,5] The region is home to 75% of global burden of HIV.[6-8] Globally, in 2016, it was estimated that 2.1 million children aged under 15 years were living with HIV with about 90% of these in sub-Saharan Africa.[7] HIV infection is a major contributor to under-five mortality in sub-Saharan Africa.[7] It is also estimated that about 80% of people living with HIV will develop a respiratory infection at some time in the course of their disease.[9,10] HIV-infected individuals also have an increased risk of diarrhoeal diseases.[11,12]

The Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) proposed vaccination as one of the key interventions against pneumonia and diarrhoea.[13] Vaccine use in Global Alliance for Vaccines and Immunisation (GAVI)-supported countries led to a drop in the child mortality rate from 76 to 63 deaths per 1,000 live births between 2010 and 2015.[14,15] In spite of the progress made in vaccination coverage in many African countries, there are still many unvaccinated and under-vaccinated children with the high possibility of the children, especially HIV-exposed children, dying from various vaccine-preventable diseases.[16,17]

Most studies on acute respiratory infections and diarrhoeal diseases among HIV-exposed children do not take immunisation status into account.[16,17] There is also a lack of information concerning morbidity differentials and benefits of immunisation among children with respect to HIV status. There is evidence that children of HIV-infected mothers are more susceptible to acute respiratory infections and diarrhoeal diseases in comparison to the HIV non-exposed children.[15,16] However, this finding is from a few observational studies mainly conducted in Africa. There is need for a large study to resolve these competing conclusions, and the Demographic and Health Survey (DHS) is a good source of data to meet this need. This research determined the prevalence of

symptoms of acute respiratory infections and episodes of diarrhoea; and assessed if there was any significant morbidity benefit conferred by diphtheria-tetanus-pertussis (DTP3) vaccination among children in sub-Saharan Africa. This study also examined if maternal HIV status affects morbidity benefits of DTP3 uptake among sub-Saharan African children. Uptake of three doses of vaccines containing DTP3 by one year of age is considered to be a proxy for the immunisation status of children.[18]

Methods

Data sources

Data sets were obtained from the DHS program,[19] United Nations Development Programs,[20] , the World Bank[21] and Joint United Nations Programme on HIV/AIDS.[4] The study countries were selected based on the availability of DHS data on childhood immunisation coverage; HIV testing; recent symptoms of acute respiratory infection and episodes of acute diarrhoea two weeks prior to the conduct of the surveys. The included countries were as follows: Angola, Burkina Faso, Burundi, Cameroon, Chad, the Democratic Republic of the Congo, Cote d'Ivoire, Ethiopia, Gabon, The Gambia, Ghana, Guinea, Kenya, Lesotho, Liberia, Malawi, Mali, Namibia, Niger, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, Swaziland, Togo, Zambia and Zimbabwe.

Variables

Main outcomes

The main outcomes for this study were recent symptoms of acute respiratory infections or episodes of diarrhoea in DTP3 vaccinated children aged 12-23 months.

Country-level factors

The following country-level characteristics were included in this study: GDP per capita, adult literacy rate, human development index (HDI), health expenditure, coverage of pregnant women who received antiretroviral drugs during pregnancy, households using an improved water source, households with improved, non-shared toilet facilities and households with daily smoking in the household.[20,22] The country-level variables were divided into low and high categories for better interpretation in relation to the policy formulation.

Data analysis

The distribution of respondents were expressed as percentages. The Pearson's chi-squared test was used for analysing the contingency tables and multiple logistic regressions to examine variations across socio-economic factors. The DerSimonian-Laird method[23] was used for the random-effects model and for the calculation of the pooled prevalence estimates. Higgin's I^2 statistics was used to describe the percentage of variation across studies.[24,25] Leave-one-country-out sensitivity analysis was used to assess the stability of the meta-analysis.[26] The level of statistical significance for the analyses was $p < 0.05$ with two-tailed comparisons. Statistical analyses were performed with Stata 14.0.[27]

Ethical considerations

This study was conducted as a secondary data analysis. Ethics approval was given for the primary data by the Ethics Committee of the ICF International, Calverton, USA and National Ethics Committee of the included countries. The study participants gave consent before participation. The participant's confidentiality was also protected and all the identifier information was removed.

Results

Description of included surveys

This study used nationally-representative DHS conducted in 27 sub-Saharan African countries. These countries were included because their individual DHS has data sets on HIV status and vaccination.

The included surveys were conducted between 2003 and 2016. Table 1 shows the year of the survey, use of antiretroviral drugs during pregnancy, gross domestic product (GDP) per capita, HDI, adult literacy rate, percentage of households using an improved water source, percentage of households with improved non-shared toilet facilities, and percentage of households in which there is daily smoking. The GDP per capita ranged from $285.7 in Burundi to $7,179.3 in Gabon. The adult literacy rate ranged from 15.5% in Niger to 88.7% in Zimbabwe. HIV prevalence among women aged 15-49 years old ranged from 0.5% in Niger to 34.7% in Swaziland. The percentage of HIV-infected women who were pregnant and received antiretroviral drugs during pregnancy

varied from 35% in Mali to 96% in Namibia. The percentage of households using an improved water source varied from 5.8% in Sao Tome and Principe to 45.9% in Angola, while households with improved and non-shared toilet facilities varied from 6.6% in Chad to 54.1% in Rwanda.

Table 2 shows the number of children who developed symptoms of acute respiratory infections and episodes of diarrhoea by DTP3 status in each country. The prevalence of acute respiratory infections among children who did not receive DTP3 varied between 6% in Angola and 79% in Burundi; and among children who received DTP3, it varied from 8% in Angola to 79% in Burundi. The combined prevalence of symptoms of acute respiratory infections in the 27 countries was 37.2% (4,523 / 12,158) among children who did not receive DTP3, and 37.4% (8,153 / 21,801) among children who received DTP3. The prevalence of episodes of diarrhoea ranged from 5% in Rwanda to 26% in Liberia among children who did not receive DTP3, and from 9% in Mali to 29% in Malawi among children who received DTP3. The combined prevalence of diarrhoea was 16.0% (6,808 / 42,592) among children who did not receive DTP3 and 17.3% (12,845 / 74,188) among children who received DTP3.

Table 1: Year of DHS survey and socio-economic characteristics of 27 study countries in sub-Saharan Africa

Country	Year of survey	GDP per capita	HDI	Adult literacy rate	Health expenditure	Antiretroviral drug coverage during PMTCT	HIV prevalence (adult female)	Households using an improved water source	Households with improved, non-shared toilet facilities	Households with smoking in the household daily
Angola	2016	3110.8	0.533	66	179.4	44	2.2	45.9	32.2	13.1
Burkina Faso	2010	649.7	0.402	34.6	35.2	83	1.1	23	15.2	n/a
Burundi	2011	285.7	0.404	61.6	21.6	84	1.3	23.4	31.4	27.3
Cameroon	2011	1032.6	0.518	71.3	58.7	74	5.1	28.4	35.9	n/a
Chad	2015	664.3	0.396	22.3	37.1	63	1.6	44.5	6.6	12.8
Congo DR	2014	444.5	0.435	77	19.1	70	1	51	18.4	23
Cote d'Ivoire	2012	1526.2	0.474	43.9	88.4	73	3.5	20.9	18	21.8
Ethiopia	2003	706.8	0.448	39	26.6	69	1.3	38.4	6.8	7.1
Gabon	2012	7179.3	0.697	82.3	321.3	76	5.3	6.2	33.7	20.2
The Gambia	2013	473.2	0.452	42	30.7	69	2	8.1	37	24
Ghana	2014	1513.5	0.579	71.5	57.9	56	2.1	10.2	13.6	9.3
Guinea	2012	508.1	0.414	32	37.3	43	1.9	25.1	19	22.8
Kenya	2009	1455.4	0.555	78.7	77.7	80	6.9	35.5	22.7	n/a
Lesotho	2014	998.1	0.497	76.6	105.1	66	29.8	16.4	47.1	16.3
Liberia	2013	455.4	0.427	42.9	46.3	70	2	27.3	14.2	12.7
Malawi	2016	300.8	0.476	62.1	29	84	11.2	12.7	51.8	12.1
Mali	2013	780.5	0.442	33.1	47.8	35	1.2	34	22	17.1
Namibia	2012	4140.5	0.64	88.3	499	96	16.6	10.4	33.5	n/a
Niger	2013	363.2	0.353	15.5	24.4	52	0.5	32.9	9.3	n/a
Rwanda	2015	702.8	0.498	68.3	52.5	82	3.8	27	54.1	14.6
Sao T&P	2009	1756.1	0.574	90.1	165.6	n/a	n/a	5.8	30.4	n/a
Senegal	2011	958.1	0.494	42.8	49.5	55	0.6	19.5	41.1	28.6
Sierra Leone	2013	496	0.42	32.4	85.9	87	2	39.1	9.6	37.6
Swaziland	2007	2775.2	0.541	83.1	247.9	95	34.7	29.9	9.3	n/a
Togo	2014	578.5	0.487	63.8	33.9	86	2.7	35.8	12.2	13.5
Zambia	2014	1178.4	0.579	83	85.9	83	14.5	34.5	25.4	n/a
Zimbabwe	2015	1008.6	0.516	88.7	57.7	93	16.1	21.8	37	10.8

GDP: gross domestic product, HDI: human development index, n/a: not available)
GDP - Low-income economies are defined as those with a GDP per capita of $1,025 or less; lower middle-income economies: $1,026 - $4,035; upper middle-income economies: $4,036 - $12,475; high-income economies: ≥ $12,476. HDI - low: <0.549; medium: 0.550 – 0.770.
(Source: Demographic and Health Surveys, World Bank, Joint United Nations Programme on HIV/AIDS, United Nations Development Program

Table 2: Number of cases and percentages of symptoms of acute respiratory infections and episodes of diarrhoea among the children with respect to DTP3 vaccination in 27 countries in sub-Saharan Africa

	Symptoms of acute respiratory infections				Episodes of diarrhea			
	DTP3 non-uptake		DTP3 uptake		DTP3 non-uptake		DTP3 uptake	
Country	**No of cases**	**Percent (%)**	**No of cases**	**Percent (%)**	**No of cases**	**Percent (%)**	**No of cases**	**Percent (%)**
Angola	164	6	92	8	417	16	264	23
Burkina Faso	60	47	231	40	175	13	865	16
Burundi	133	79	908	79	85	20	812	26
Cameroon	267	56	470	45	329	20	559	18
Chad	381	58	154	57	759	19	274	19
Congo DR	566	42	513	37	765	18	685	16
Cote d'Ivoire	132	49	163	41	260	19	361	19
Ethiopia	786	60	417	59	1069	16	492	14
Gabon	344	42	206	40	431	19	202	16
The Gambia	65	71	236	62	133	17	513	19
Ghana	32	49	149	47	40	6	293	14
Guinea	259	68	168	61	314	17	229	16
Kenya	88	49	258	50	123	18	323	17
Lesotho	16	27	117	36	25	9	137	12
Liberia	205	48	256	49	374	26	427	23
Malawi	60	11	354	14	80	15	762	29
Mali	57	45	92	41	153	7	249	9
Namibia	153	51	198	44	281	13	478	15
Niger	46	39	210	43	63	15	328	20
Rwanda	20	38	382	42	14	5	424	12
Sao T&P	30	57	175	53	40	13	184	13
Senegal	115	65	366	60	213	21	603	20
Sierra Leone	176	66	437	62	137	10	410	12
Swaziland	45	54	308	54	41	12	287	15
Togo	103	54	373	53	102	14	431	17
Zambia	151	33	680	30	272	12	1679	18
Zimbabwe	69	9	240	10	113	15	574	24

Table 3 shows the number of cases of acute respiratory infections and episodes of diarrhoea among children who received DTP3, grouped by the HIV status of their mothers. Among the children who received DTP3, the prevalence of symptoms of acute respiratory infections varied between 9% in Mali and 24% in Zimbabwe for children of HIV-uninfected mothers; and between 4% in Ethiopia

and 30% in Chad for children of HIV-infected mothers. The combined prevalence of acute respiratory infections among children who received DTP3 was 38.0% (7,726 / 20,320) for children born of HIV-uninfected mothers and 28.8% (427/ 1481) for children of women living with HIV.

Regarding episodes of diarrhoea among children who received DTP3, the prevalence varied between 8% in Angola and 79% in Burundi in children of HIV-uninfected mothers; and between 0% in Namibia and 73% in Sierra Leone among the children of HIV-infected mothers. The combined prevalence of diarrhoea among children who received DTP3 was 17.4% (12,184 / 70,161) for children born of HIV-uninfected mothers and 16.4% (661 / 4,027) for children of mothers living with HIV.

Table 3: Number of cases and percentages of symptoms of acute respiratory infections and episodes of diarrhoea among the children with uptake of DTP3 and maternal HIV status in 27 countries in sub-Saharan Africa

	Symptoms of acute respiratory infections				Episodes of diarrhea			
	HIV-uninfected		HIV-infected		HIV-uninfected		HIV-infected	
Country	No of cases	Percent (%)	No of cases	Percent (%)	No of cases	Percent (%)	No of cases	Percent (%)
Angola	258	23	6	29	91	8	1	5
Burkina Faso	857	16	8	16	228	40	3	50
Burundi	789	26	23	30	887	79	21	70
Cameroon	536	18	23	16	451	45	19	46
Chad	266	19	8	30	150	58	4	50
Congo DR	681	16	4	11	507	37	6	33
Cote d'Ivoire	355	19	6	10	160	42	3	30
Ethiopia	489	14	3	4	413	59	4	33
Gabon	198	16	4	8	198	40	8	36
Gambia	505	19	8	20	233	63	3	60
Ghana	290	14	3	7	144	47	5	50
Guinea	222	16	7	29	164	61	4	57
Kenya	291	17	32	22	237	50	21	51
Lesotho	105	13	32	11	92	36	25	36
Liberia	425	23	2	10	254	49	2	33
Malawi	712	30	50	25	330	14	24	12
Mali	246	9	3	11	90	41	2	40
Namibia	476	15	2	12	198	44	0	0
Niger	271	20	57	21	172	43	38	44
Rwanda	412	12	12	10	370	42	12	48
Sao T&P	183	13	1	8	175	53	n/a	n/a
Senegal	602	20	1	5	365	60	1	33
Sierra Leone	407	12	3	7	429	62	8	73
Swaziland	200	16	87	14	205	54	103	55
Togo	421	17	10	17	363	54	10	44
Zambia	1,485	18	194	17	608	30	72	27
Zimbabwe	502	24	72	20	212	10	28	8

Association between DTP3 status and acute respiratory infections or diarrhoea

Figures 1 and 2 are forest plots of meta-analyses of the association between DTP3 status and acute respiratory infections or diarrhoea in each country at the time of the surveys. The combined result

shows that children who did not receive DTP3 were more likely to have symptoms of acute respiratory infections than children who had DTP3: odds ratio (OR) 1.09, 95% confidence interval (CI) 1.02 to 1.17). There was low heterogeneity in results across countries (I^2 = 32.6%) (Figure 1).

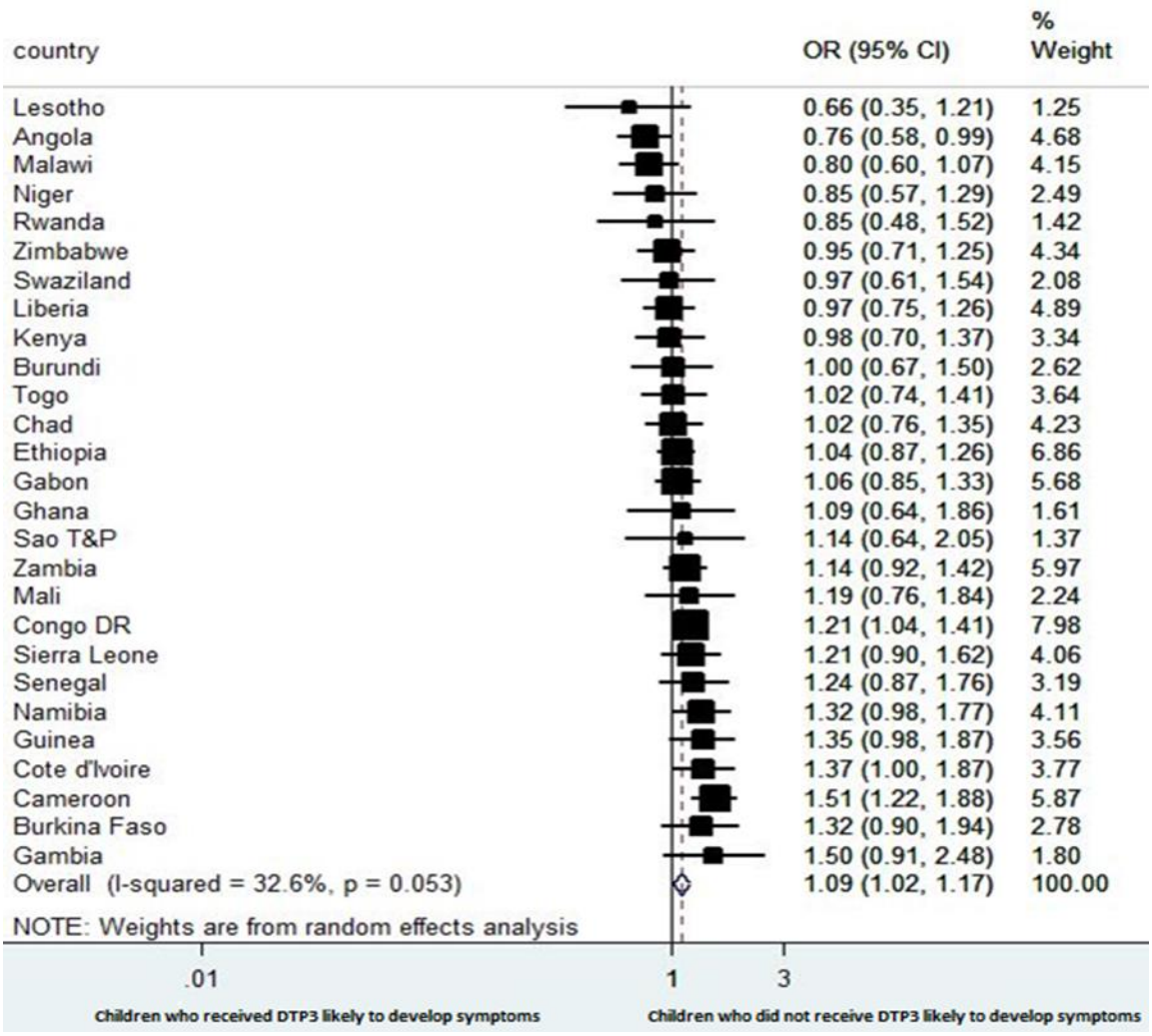

Figure 1: Forest plot showing the prevalence of estimates of symptoms of acute respiratory infections among the children with respect to DTP3 vaccination in 27 sub-Saharan Africa countries

The combined result for diarrhoea shows that children who did not receive DTP3 were less likely to have episodes of diarrhoea at the time of the survey than children who received DTP3 (OR 0.83, 95% CI 0.74 to 0.92); with substantial heterogeneity in results across countries (I^2 = 88.3%) (Figure 2).

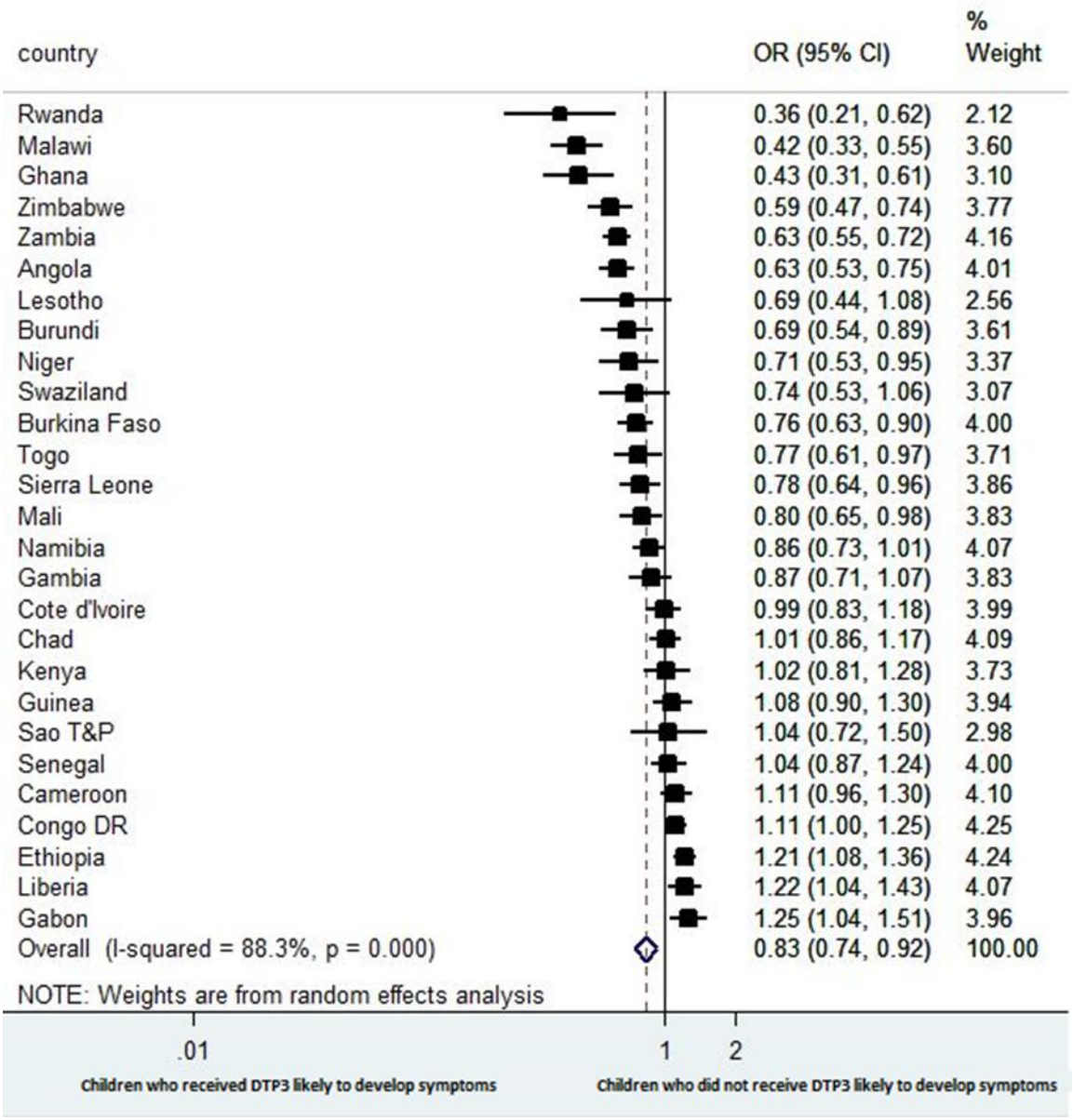

Figure 2: Forest plot showing the prevalence of estimates of episodes of diarrhoea among the children with respect to DTP3 vaccination in 27 sub-Saharan Africa countries

Figure 3 shows estimates of the association between receipt of DTP3 and presence of symptoms of acute respiratory infections among the children of HIV-infected mothers in each country at the time of the survey. The pooled result shows no significant difference in the odds of having symptoms of acute respiratory infections between children who did not receive and those who

received DTP3 (OR 0.99, 95% CI 0.74 to 1.32), with low heterogeneity across countries (I^2 = 0.0%). Only 19 countries were included in this analysis.

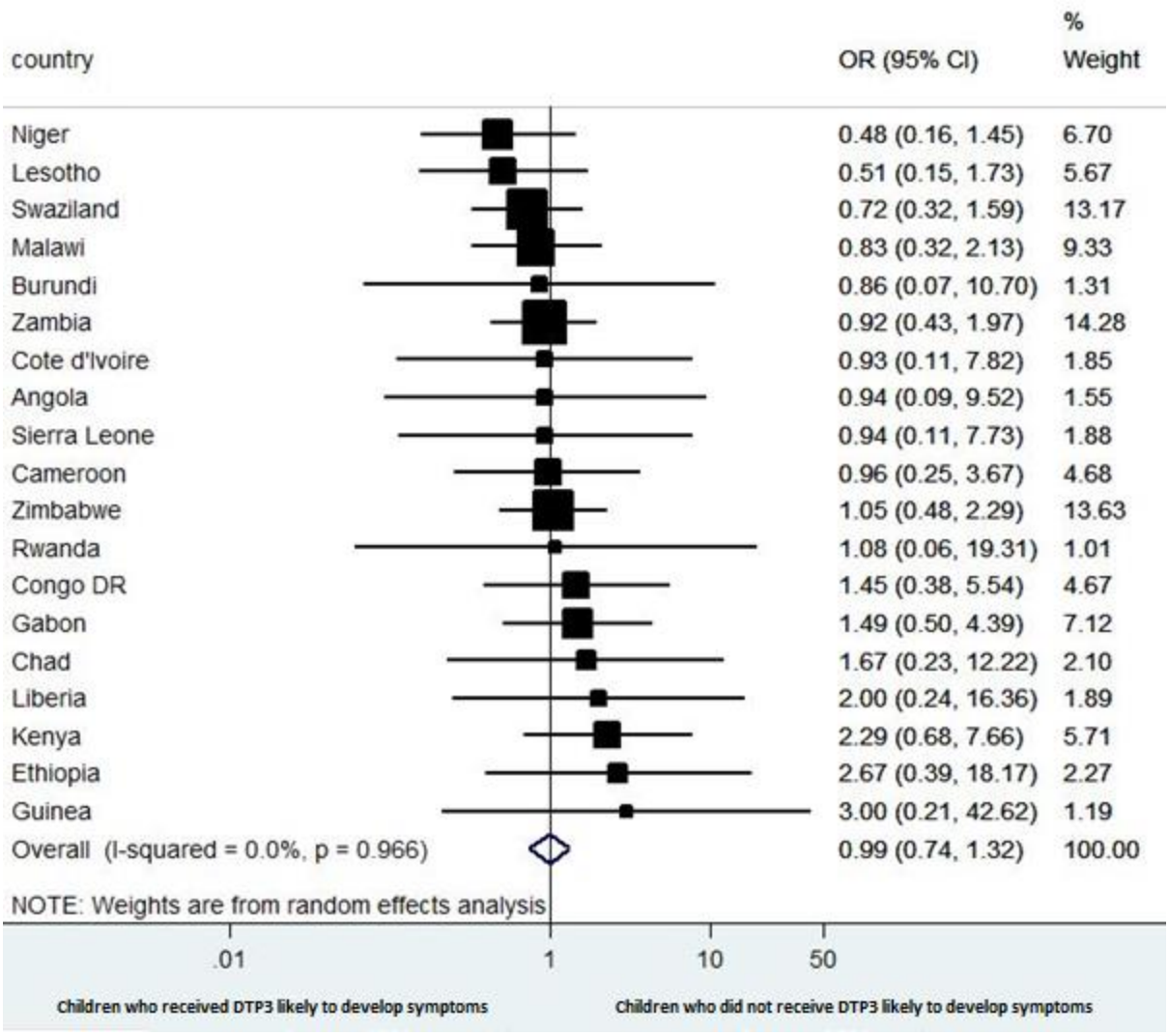

Figure 3: Forest plot showing the prevalence of estimates of symptoms of acute respiratory infections among the children of HIV-infected mothers with respect to DTP3 vaccination in selected sub-Saharan Africa countries

Figure 4 shows estimates of the association between receipt of DTP3 and episodes of diarrhoea among the children of HIV-infected mothers at the time of the survey in each country. The combined result shows no difference in the occurrence of episodes of diarrhoea between children

who did not receive DTP3 and those who received DTP3 (OR 0.85, 95% CI 0.62 to 1.07), with low heterogeneity across countries (I^2 = 11.1%). Only 24 countries were included in this analysis.

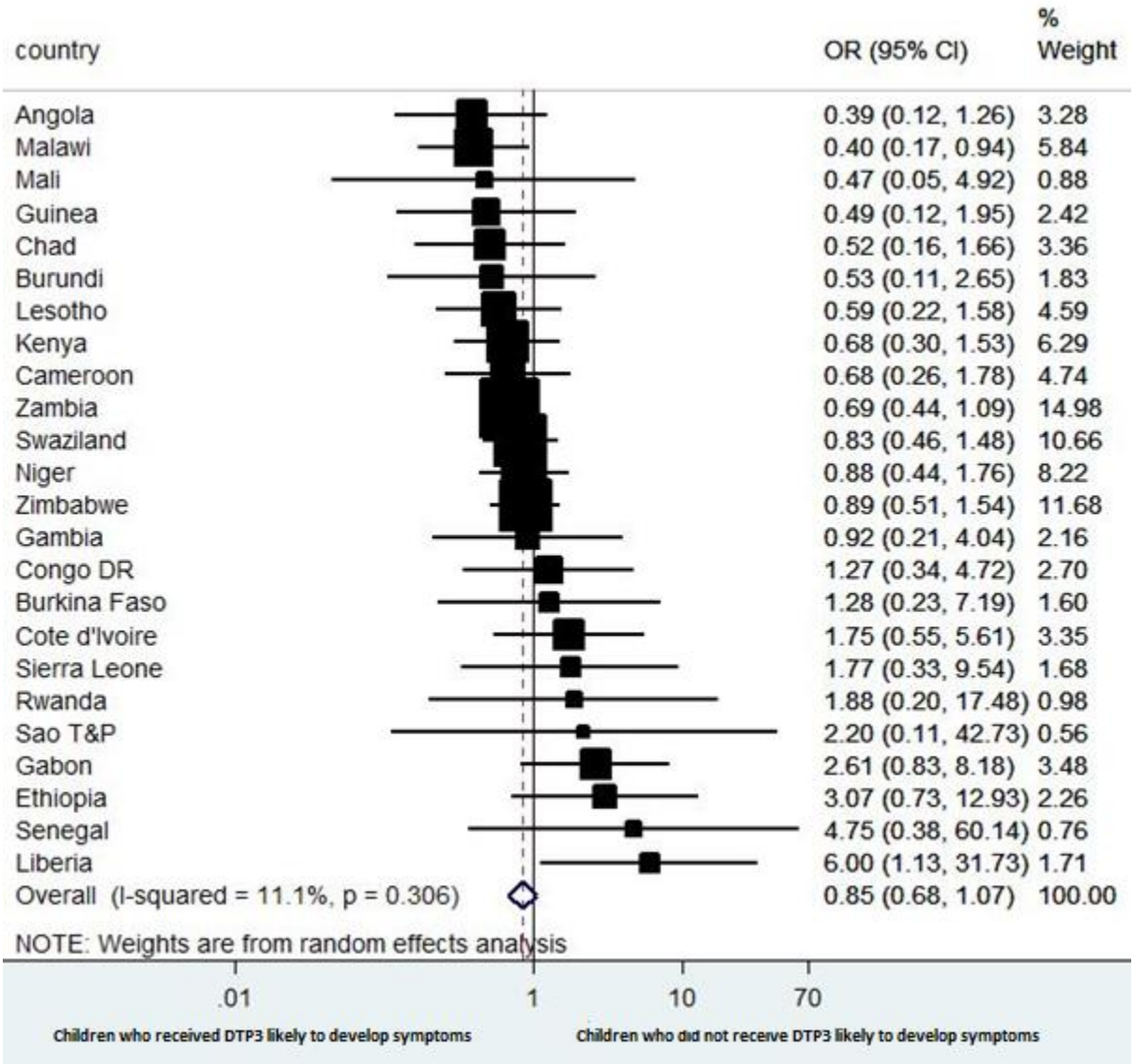

Figure 4: Forest plot showing the prevalence of estimates of episodes of diarrhoea among the children of HIV-infected mothers with respect to DTP3 vaccination in selected sub-Saharan Africa countries

When we combined the data for the prevalence of symptoms of acute respiratory infections across the study countries, there was no significant difference between the children of HIV-uninfected mothers who were vaccinated with DTP3 and those of mothers living with HIV (OR 1.04, 95% CI

0.86 to 1.26); with low heterogeneity across countries (I^2 = 0.0%) (Figure 5). Similarly, there was no difference in the combined prevalence of episodes of diarrhoea between the children of HIV-uninfected mothers who were vaccinated with DTP3 and those of mothers living with HIV (OR 0.90; 95% CI 0.80 to 1.01); with low heterogeneity in results among countries (I^2 = 18.4%) (Figure 6).

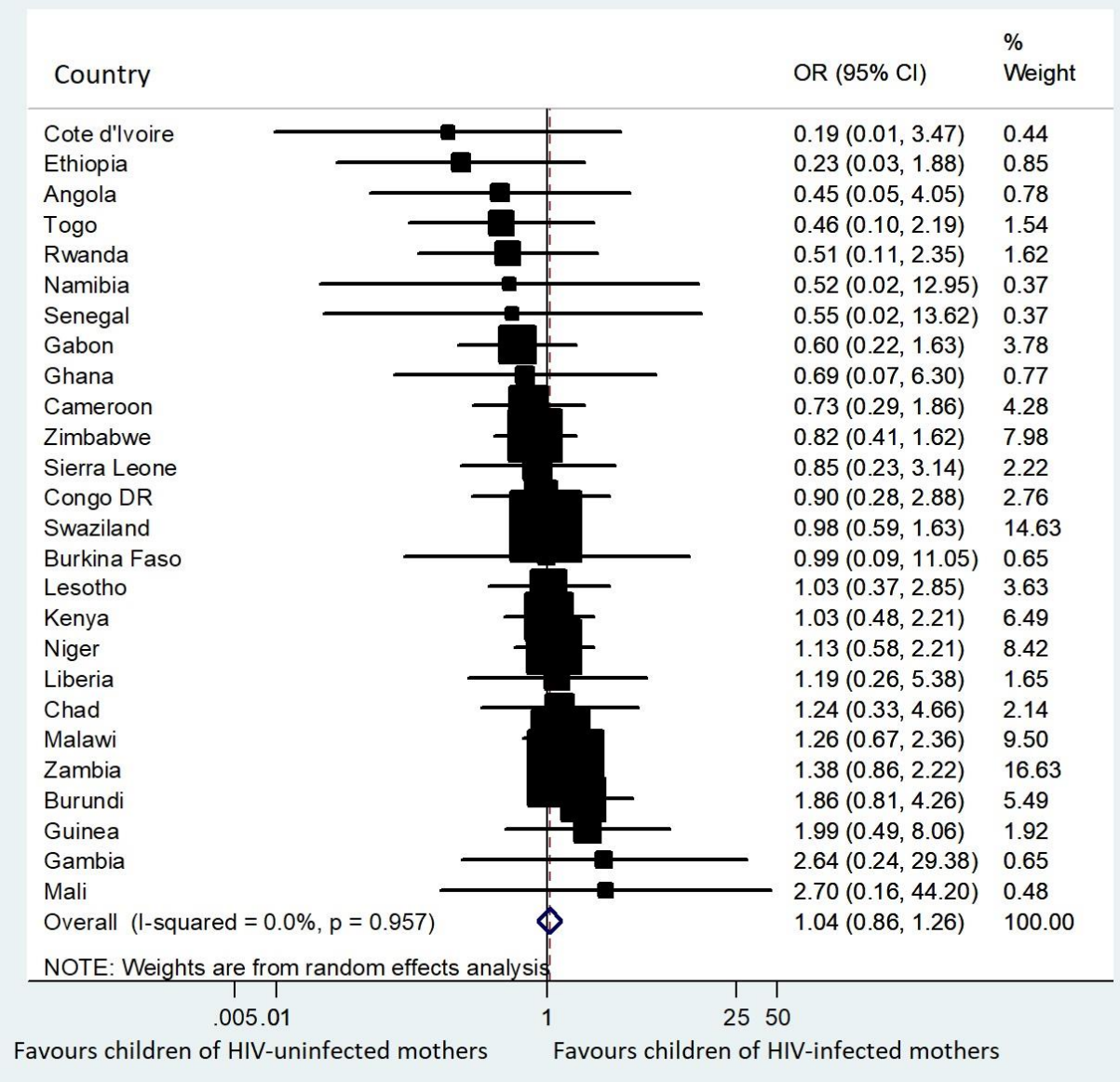

Figure 5: Forest plot showing the prevalence of estimates of symptoms of acute respiratory infections among the children who were vaccinated with DTP3 with respect to the maternal HIV status in 27 sub-Saharan Africa

countries

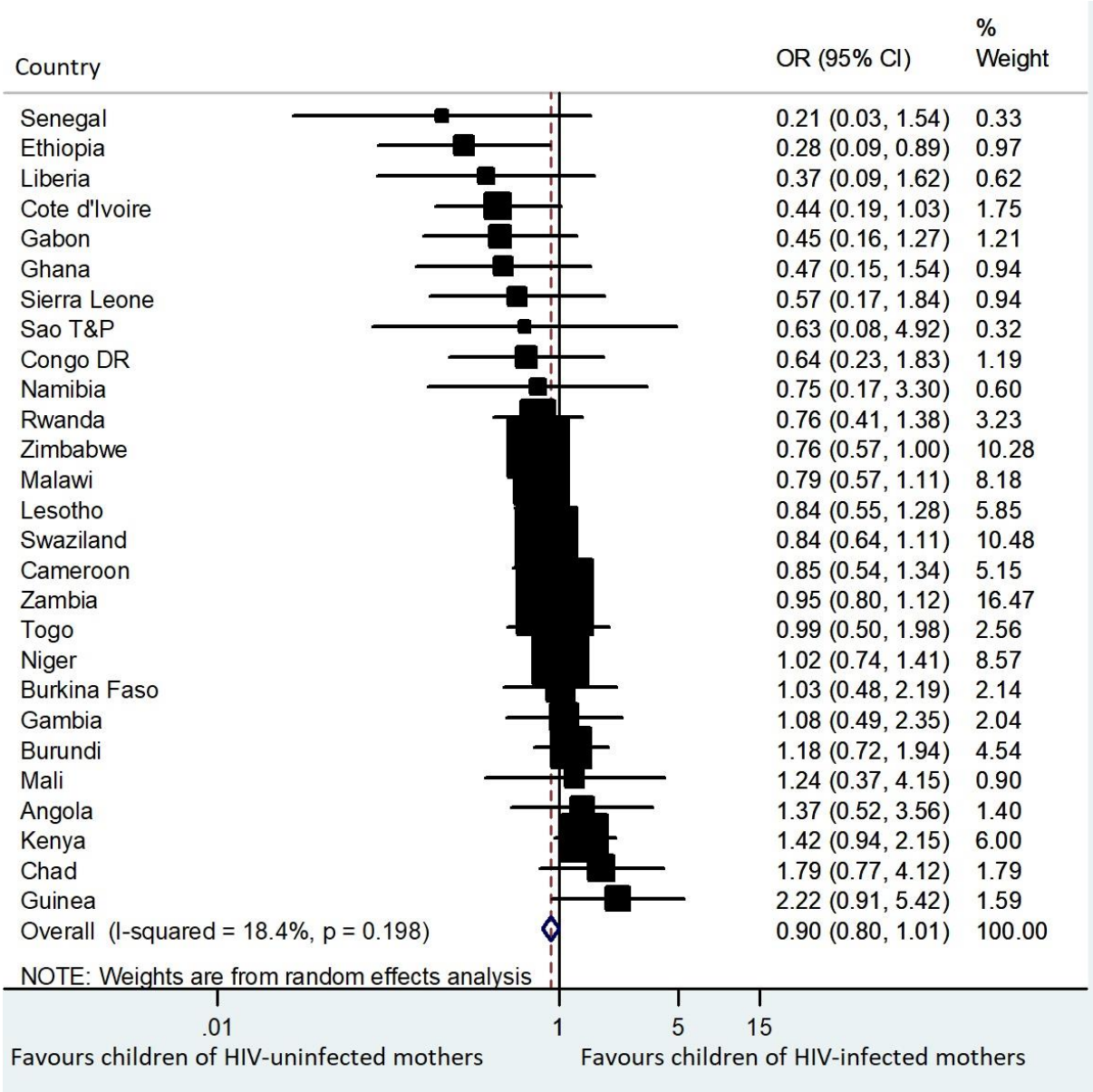

Figure 6:Forest plot showing the prevalence of estimates of episodes of diarrhoea among the children who were vaccinated with DTP3 with respect to the maternal HIV status in 26 sub-Saharan Africa countries

Leave-one-country-out sensitivity analyses show that no country had an undue influence on the pooled estimate of episodes of acute respiratory infections and diarrhoea (Figures 7 and 8). The variations in the CIs with the exclusion of each country remains within the 95% confidence interval for the overall estimates. The stability of the overall results for both episodes of acute respiratory infections and diarrhoea was justified by the outcome of the sensitivity analyses.

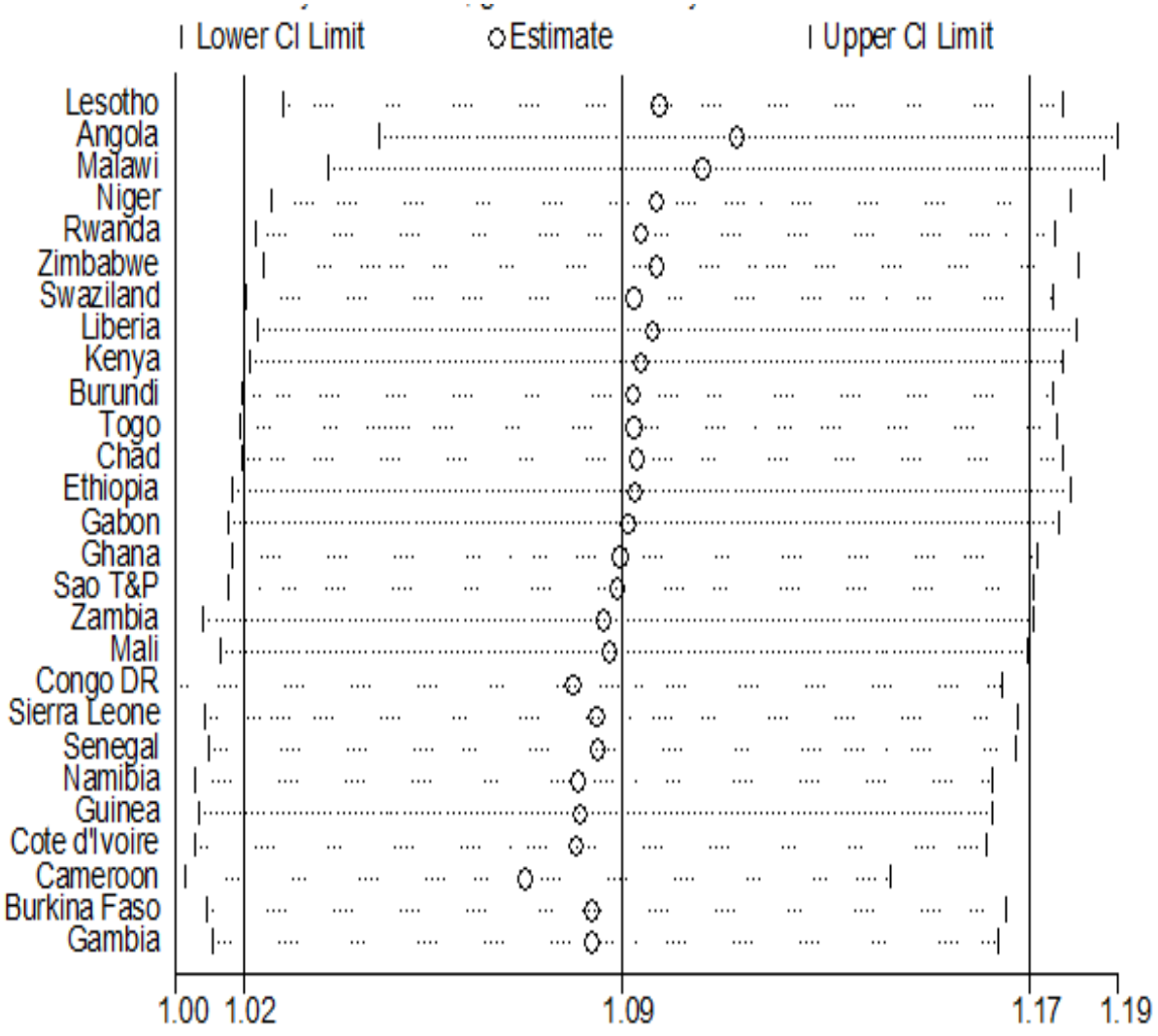

Figure 7: A plot showing the influence of each country on the overall pooled result for estimates of acute respiratory infections using 'leave-one-country-out' sensitivity analysis

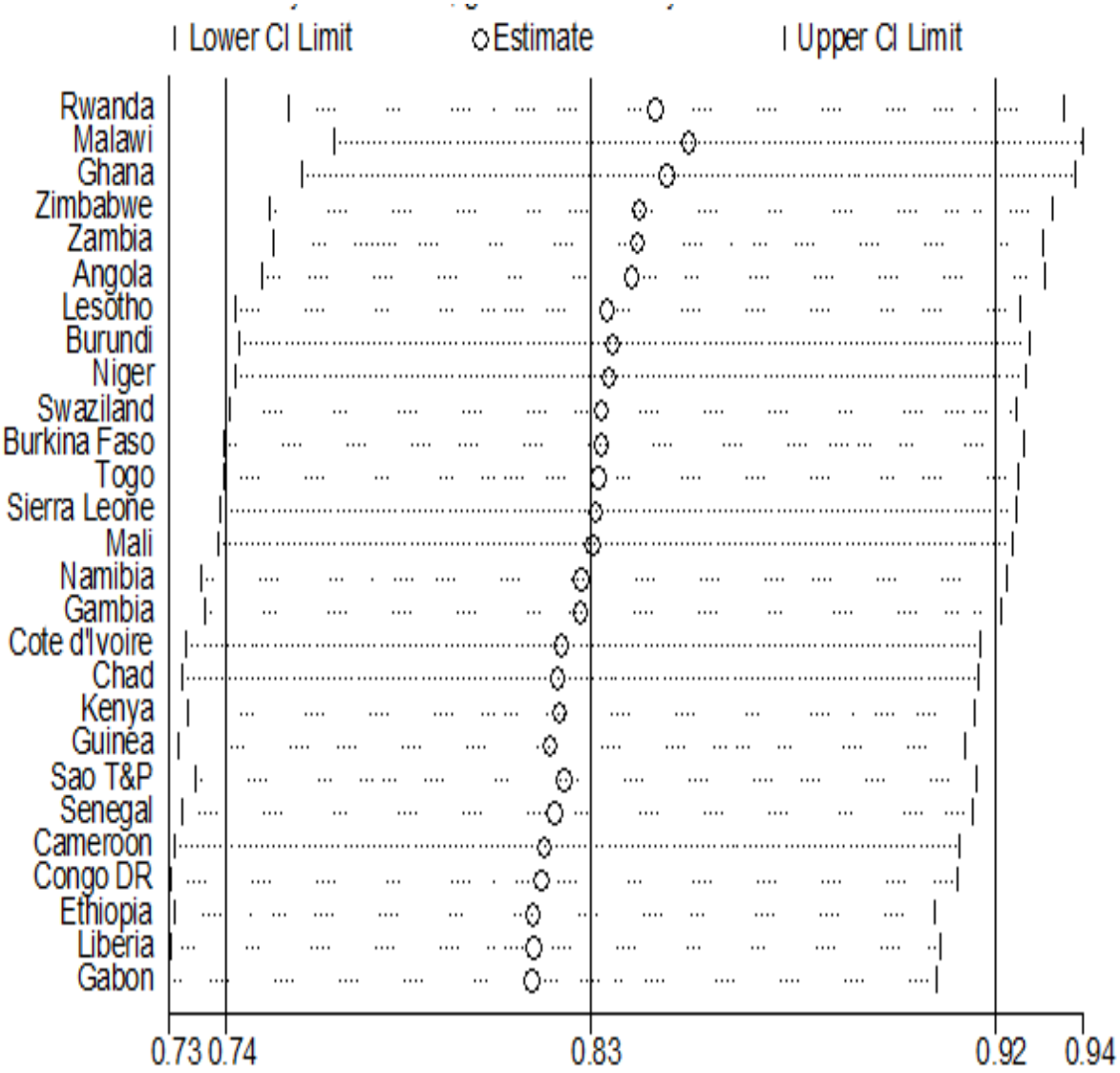

Figure 8: A plot showing the influence of each country on the overall pooled result for estimates of diarrhoea using 'leave-one-country-out' sensitivity analysis

Sub-group analyses

In order to assess the effect of various country-level characteristics on the pooled estimates, subgroup analyses were conducted using the DerSimonian-Laird method. Results from the subgroup analyses show that the differences between countries in HDI, GDP, adult literacy rate, years of survey, sub-regions (West Africa, Central/East Africa, Southern Africa), households using an improved water source, and households with improved non-shared toilet facilities did not explain the heterogeneity of estimates of episodes of diarrhoea among the children (Table 4).

Meta-regression analysis

Meta-regression analyses were conducted to investigate which country-level characteristics might account for the heterogeneity in the association between receipt of DTP3 and prevalence of diarrhoea (Figure 2). Table 4 shows that year of the survey was a significant predictor of the association between DTP3 uptake and diarrhoea. HDI, GDP, adult literacy rate, sub-regions, households using an improved water source, and households with improved non-shared toilet facilities were not significantly associated with the episodes of diarrhoea in children vaccinated with DTP3 (Table 4).

Table 4: Subgroup analysis and the univariate meta-regression analysis results (for diarrhoea)

Characteristics	No of studies	Subgroup odds ratio	95% CI	I-squared	P-value*	Univariate meta-regression	
						#β (p-value)*	95% CI
Year of survey						0.95 (0.009)	0.91,0.99
2003-2007	2	0.98	0.61, 1.57	85.2	0.000		
2008-2012	10	0.97	0.87, 1.09	70.0	0.000		
2013-2016	15	0.72	0.61, 0.85	90.1	0.000		
Gross domestic product per capita (US$)						0.98 (0.862)	0.75, 1.28
Low	18	0.84	0.73, 0.95	87.8	0.000		
Middle	9	0.83	0.67, 0.99	88.1	0.000		
Human development index						1.01 (0.950)	0.74, 1.37
Low	21	0.83	0.73, 0.93	87.6	0.000		
Medium	6	0.83	0.62, 1.09	90.7	0.000		
Adult literacy rate						1.00 (0.273)	0.99, 1.00
Low	11	0.95	0.85, 1.06	77.4	0.000		
Average	9	0.70	0.54, 0.90	86.8	0.000		
High	7	0.80	0.64, 1.02	92.4	0.000		
Households using an improved water source						1.12 (0.356)	0.87, 1.44
Low	12	0.77	0.65, 0.92	87.1	0.000		
Medium	15	0.87	0.76, 1.00	88.8	0.000		
Households with improved, non-shared toilet facilities						0.85 (0.195)	0.67, 1.09
Low	14	0.90	0.80, 1.02	82.9	0.000		
Medium	13	0.76	0.63, 0.91	89.5	0.000		
Regions						0.88 (0.073)	0.76, 1.01
Western Africa	13	0.88	0.78, 0.99	76.9	0.000		
Central/Eastern Africa	7	1.00	0.85, 1.17	82.5	0.000		
Southern Africa	7	0.64	0.54, 0.75	75.5	0.000		

* $p < 0.05$ #β- Beta coefficient

Discussion

This research illustrates that DTP vaccination had some benefit in terms of reduced odds of developing acute respiratory infections but not for diarrhoeal episodes among children in sub-Saharan Africa. We found no significant difference in the estimates of having symptoms of acute respiratory infections and episodes of diarrhoea among the DTP3 vaccinated children of HIV-infected mothers and HIV-uninfected mothers. Morbidity benefit in terms of acute respiratory infections and diarrhoea varied across sub-Saharan African countries. The prevalence of acute respiratory infections was higher among the vaccinated children of HIV-uninfected mothers than the children of HIV-infected mothers. The children of HIV-uninfected women also had more episodes of diarrhoea than the vaccinated children of women living with HIV.

This research contrasts with the findings of a Malawian study among HIV-infected, HIV-exposed uninfected and HIV-unexposed children which showed morbidity benefit for both diarrhoea and respiratory infection among the children of HIV-uninfected mothers.[17] A cohort study of a Congolese birth cohort of 429 infants born to HIV-infected and HIV-uninfected mothers shows that two-thirds of the infant had at least one episode of acute diarrhoea within the 16-month study period.[28] The study showed that HIV-infected children had diarrhoea incidence of 170 episodes per 100 child-years while the uninfected infants had 100 per 100 child-years.[28] However, both HIV-exposed uninfected children and the infants of HIV-uninfected mothers had similar overall diarrhoeal incidence rates.[28] Findings from a South African study among breastfed infants revealed that there were more cases of severe infectious morbidity among HIV-exposed infants than the HIV-uninfected infants who were breastfed.[29] However, there was no significant difference between the HIV-exposed and HIV-uninfected infants with respect to infectious causes leading to hospitalisation or mortality at six months of life.[29] It should be noted that unlike the respondents of this particular study who were all vaccinated with DTP3, the participants of the Congolese and South African studies had varying coverage of vaccination.[28,29]

Meta-regression analyses were conducted to assess the relationship between various covariates and the dependent variables. The meta-regression analytic findings for episodes of diarrhoea were not significant for the country-level characteristics except for the year of the survey. The included surveys were conducted over a decade and the long span of time between the surveys could explain

the significant heterogeneity finding of the meta-analysis for the estimates of episodes of diarrhoea among sub-Saharan African children. The meta-regression findings show that the year of survey is an important predictor of episodes of diarrhoea as it relates to uptake of DTP3. There have been progressive changes in terms of healthcare coverage, introduction of newer vaccines, etc. in different countries over the years and this could well explain the widely varying changes in episodes of diarrhoea over the years.

Vaccination against vaccine-preventable diseases is not the only factor linked to the occurrence of diarrhoea and respiratory infections. The state of health care infrastructure and lack of resources could be one of the reasons for the huge differences in the prevalence of acute respiratory diseases and diarrhoea among the African countries. Improved water supply is linked to reduction in episodes of diarrhoea.[30] It has been proven that households with improved water supply could reduce incidence of diarrhoea among under-five children in sub-Saharan Africa.[30] The use of pipe-borne water supply within a private household or yard is a major source of improved water supply. Other improved drinking water sources are public water taps, protected deep wells, boreholes, collected rainwater and protected springs.[31] Diarrhoeal diseases could be reduced by 11% if the users of unimproved water sources switched to improved water sources and by 23% if switched to private household piped water.[32] The use of water treatment such as boiling, filtration and proper storage could reduce diarrhoea by 45%.[32] Consistent handwashing with soap could reduce the risk of diarrhoeal disease by at least 48%.[33] Moderate-severe diarrhoea is also reduced by the use of private household toilet in comparison to sharing with other households.[34]

Smoking is a major risk factor for respiratory tract infections secondary to bacterial and fungal agents. There is an increased risk of respiratory tract infections due to both active and passive smoke exposures. There are strong links between smoking and serious respiratory infections such as invasive pneumococcal disease, influenza and tuberculosis.[35] Indoor air pollution particularly from the use of household biomass fuels is linked to respiratory tract infections and is a contributory factor to these infections in children.[36]

Policy implications

Implementation of GAPPD is essential in ending preventable childhood deaths due to pneumonia and diarrhoea by 2025.[13] Tackling various causes and risk factors for respiratory-tract infections and diarrhoeal diseases should be a priority for various stakeholders in sub-Saharan Africa. There is need for the introduction and scaling up of the use of newer vaccines such as *Haemophilus influenzae* type B, pneumococcus, and rotavirus vaccines especially in African countries that are yet to include them in their national immunisation programmes. Rotavirus is the most common cause of severe and fatal diarrhoea in children while *Streptococcus pneumonia* and *Haemophilus influenzae* cause pneumonia, meningitis, otitis media, sinusitis, etc. in children.[37,38] The inclusion of these newer vaccines will further reduce the incidence of diarrhoea and pneumonia. African government officials, policy makers, developmental agencies and healthcare workers should ensure the availability and easy access to routine licensed vaccines. The health systems in some African countries are very weak and need to be strengthened with efforts channelled towards improving low vaccination coverage.[14,39] In addition to ensuring optimal immunisation programming, there is also need to promote other strategies such as vitamin-A supplementation, use of zinc supplements, the prevention of low birth weight, breastfeeding, personal hygiene and weaning education.[40]

Investing in various methods of effective household water treatment in combination with proper safe water storage can lead to substantial reductions in cases of diarrhoeal diseases. The provision and use of improved toilet facilities in households can also lead to further reduction in diarrhoea among African children. Prevalence of handwashing is very low in most low- and middle-income countries which are also the countries with the highest levels of pneumonia and diarrhoea. There is also need to reduce household air pollution with the provision and use of improved stoves which has been shown to reduce severe pneumonia.[13]

Strengths and limitations

This study used DHS data which are based on countrywide surveys and therefore have advantages over primary studies which are limited to just a few communities. The meta-analyses permitted the synthesis of different findings across countries and gave room for assessment across various surveys.[41] DHS provides a good source for large maternal HIV and child immunisation data sets and the ability to merge mother and child data.

The use of rotavirus and pneumococcal vaccination data would have provided some additional information with respect to incidence of diarrhoea and pneumonia. However, the majority of the DHSs did not include these newer vaccines as, at the time of the DHS, most countries had not adopted the vaccines as part of the national immunisation programmes. The use of DTP3 is expected to reflect the national vaccination coverage since it is the benchmark for the national programme. However, one of the reasons for lack of significant association of DTP3 with reduced acute respiratory infections and diarrhoea could be that the immunisation programmes have expanded, and DTP3 may not be an accurate indicator for protection against vaccine-preventable diseases, e.g. diarrhoea, respiratory infections, measles, etc. thus the need for more indicators for childhood immunisation.

As this study is an ecological study with cross-sectional design, care must be taken in crediting detected causal relationship directly to this study. This study was limited by the non-availability of data on children's HIV status and had to use maternal HIV as a reference for the children's HIV status. The surveys were conducted over a decade and this is likely to have some influence on the study findings. Three of the meta-analyses did not include all the 27 study countries due to non-availability of data sets on episodes of diarrhoea and symptoms of acute respiratory infections especially in children of women living with HIV.

Conclusions

In conclusion, the prevalence of acute respiratory infections and diarrhoea were similar between the children who were vaccinated and those who were not vaccinated with DTP3. Both the symptoms of acute respiratory infections and episodes of diarrhoea among DTP3 vaccinated and unvaccinated children shows significant differences in the overall estimates between the two groups of children. The data for symptoms of acute respiratory infections were pooled together with no statistical difference in the overall estimates between the children of HIV-infected mothers that were vaccinated with DTP3 and those who were not vaccinated. The data for episodes of diarrhoea were pooled together with resultant nil significant difference in the overall estimates between the children of HIV-infected mothers who were vaccinated with DTP3 and the ones who were not vaccinated. There was no significant difference in the overall estimates between the children of HIV-uninfected mothers who were vaccinated with DTP3 and those of mothers living

with HIV with respect to the prevalence of symptoms of acute respiratory infections and episodes of diarrhoea across the study countries. Many African countries recorded high rates of respiratory infections and diarrhoeal diseases. Extra efforts should be targeted at tackling various causes and risk factors for respiratory-tract infections and diarrhoeal diseases especially among HIV-exposed children in sub-Saharan Africa.

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome

ARV: Antiretroviral drugs

CI: Confidence intervals

DHS: Demographic and Health Survey

DTP: Diphtheria-tetanus-pertussis

GAPPD: Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea

GAVI: Global Alliance for Vaccines and Immunisation

GDP: Gross domestic product

HDI: Human Development Index

HIV: Human Immunodeficiency Virus

OR: Odds ratio

PMTCT: Prevention of mother-to-child transmission.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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Contributions

OOA and OAU conceived the study. OOA did the data analysis, interpreted the results and wrote the initial manuscript. OAU and CSW reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

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CHAPTER 7: Non-specific effects of childhood vaccines on acute childhood morbidity among HIV-exposed children in sub-Saharan Africa: a multilevel analysis

Olatunji O. Adetokunboh, Olalekan A. Uthman and Charles S. Wiysonge

Abstract

We examined the roles of determining factors responsible for acute respiratory infections and diarrhoea among immunised human immunodeficiency virus (HIV)-exposed children in sub-Saharan Africa. This study used demographic and health surveys obtained from 27 sub-Saharan African countries. The outcome variable is defined as symptoms of acute respiratory infections or episodes of diarrhoea in the child of an HIV-infected mother who is vaccinated with the third dose of diphtheria-tetanus-pertussis containing vaccines. Multivariable logistic regression models were used to analyse the association between individual and contextual factors. The odds of developing symptoms of acute respiratory infections increased among those living in communities with high unemployment rates (Odds ratio = 1.15, 95% credible interval 1.05 to 1.26). The odds of developing diarrhoea increased among young mothers such that children of women aged 15-24 years were two times more likely to develop diarrhoea compared to children of women aged 35-49 years (Odds ratio = 2.22, 95% credible interval 1.66 to 2.93). Public healthcare programmes should target adolescent and young women, and their family members on how to prevent diarrhoea. Efforts should be made to identify the hotspots for the development of acute respiratory diseases especially in communities with high rates of unemployment and to develop strategies to combat the diseases in such communities. Initiatives such as the integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea which recommends an interrelated approach for the elimination of preventable diarrhoea and pneumonia deaths should be adopted.

***Keywords*:** Acute respiratory infections; diarrhoea; HIV; sub-Saharan Africa; demographic and health surveys; multilevel analysis.

Background

Acute diarrhoea disease and pneumonia are major causes of morbidity and mortality among children especially among the human immunodeficiency virus (HIV)-exposed and infected ones.[1] Acute respiratory infections and diarrhoeal diseases are vaccine-preventable diseases and are avoidable if children are properly immunised.[1,2] In addition to diarrhoea and pneumonia, HIV still contributes substantially to child mortality especially in Africa and South East Asia which are the regions with the highest burden of HIV.[3,4]

Immunisation programmes have proven to be a successful and cost-effective global public health interventions.[5,6] The Expanded Programme on Immunization (EPI) has led to considerable declines in the morbidity and mortality attributed to vaccine-preventable diseases.[7] Global Alliance for Vaccines and Immunisation (GAVI) initiatives have been recording reductions in childhood morbidity and mortality due to vaccine-preventable diseases among supported countries primarily as a result of vaccines use.[2] More disease and death could be averted if there is an improvement in the global vaccination coverage.[2] Africa accounts for a substantial proportion of the global vaccine-preventable diseases burden and for the highest proportion of under-five mortality from these diseases.[8,9] Meanwhile, only 74% of the World Health Organization (WHO) African member states achieved ≥ 90% national coverage for the three doses of diphtheria-tetanus-pertussis vaccines (DTP3) by 2016.[2]

Understanding the association between HIV status, uptake of childhood vaccination, acute respiratory infections and diarrhoeal diseases is of great importance in countries with high HIV prevalence especially in the sub-Saharan African region. Despite the high prevalence of HIV in many African countries, HIV testing is still not optimal. Knowledge of status among people living with HIV ranged between 29-87%. There is lack of information on socio-economic factors such as employment status, education status, mother's age, wealth index and residence which are the likely determinants of morbidities like acute respiratory infections, diarrhoeal diseases, fever, etc. among the immunised children of HIV-infected mothers. Adequate knowledge of these determining factors is crucial in making recommendations concerning public-health interventions

for the prevention of acute respiratory infections and diarrhoeal diseases among immunised and HIV-exposed children.

We examined the roles of the socio-economic factors in relation to uptake of DTP3 vaccines among HIV-exposed children. DTP3 is a key indicator used for assessing the effectiveness of childhood immunisation services. DTP can prevent diphtheria, pertussis and tetanus in children. DTP-containing vaccines are given in three doses with three booster doses and diphtheria toxoid-containing vaccines given to the older children as a booster vaccine.[10] A multilevel study was designed to assess the independent contributions of individual, community, and country-level socio-economic factors. We also developed and tested a model for the determinants as they relate to non-uptake of DTP3 vaccines among HIV-exposed children (Figure 1).

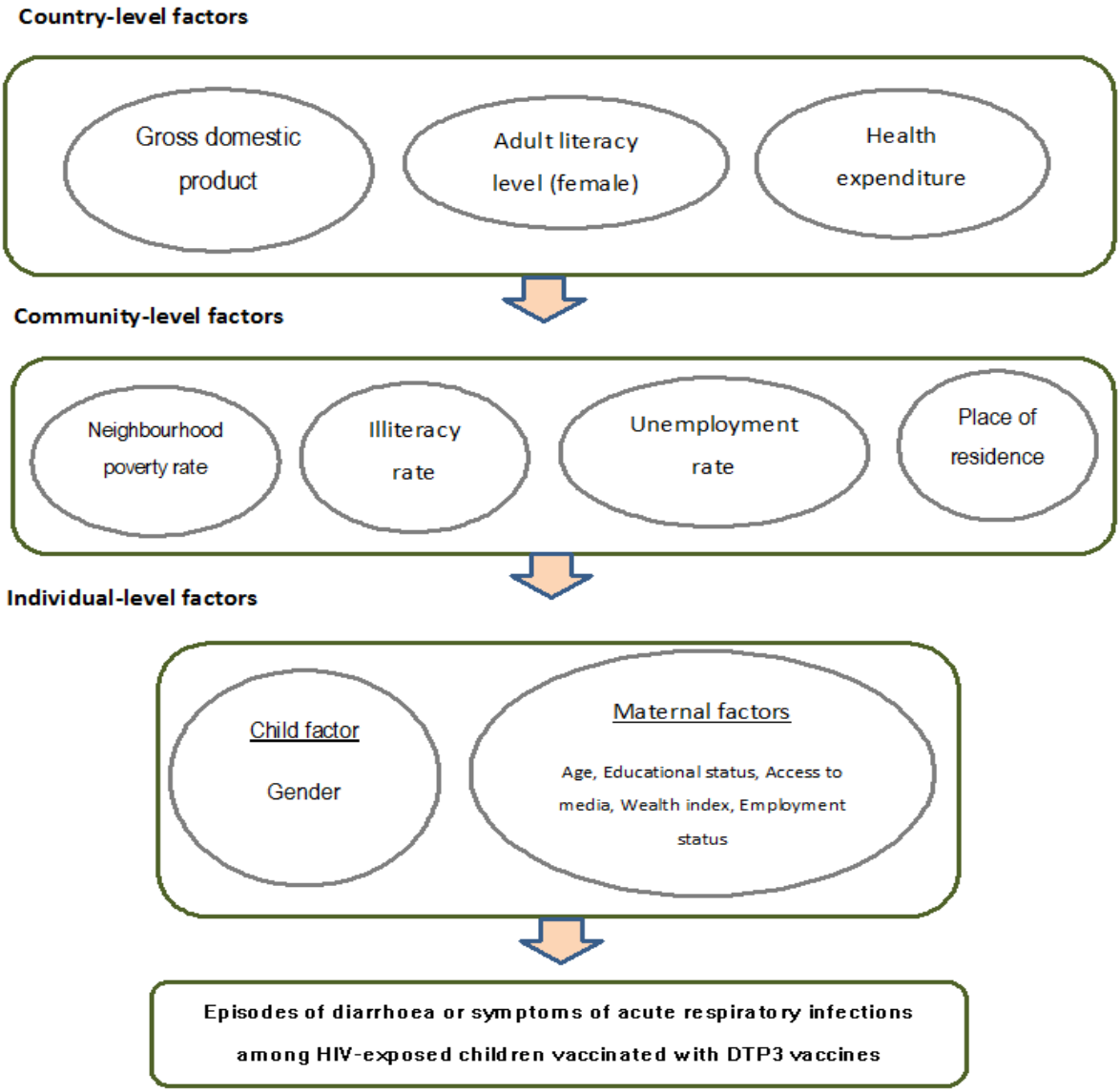

Figure 1: Conceptual framework showing the factors determining episodes of diarrhoea or symptoms of acute respiratory infections among HIV-exposed children vaccinated with DTP3 vaccines

Methods

Data sources

This study used 27 nationally represented and cross-sectional surveys as of November 2017. The Demographic and Health Surveys (DHS) were implemented by different national institutions and ICF International, Calverton, Maryland, USA. The United States Agency for International Development, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and others provided financial support. The survey methods and data-collection procedures were described in another publication.[11] Included DHS were selected based on the availability of data on childhood immunisation, maternal HIV status, symptoms of acute respiratory infections and diarrhoea. DHS data were household sample surveys and the sampling design involved selecting and interviewing samples of women aged 15–49 years based on multi-stage cluster sampling. The DHS instruments were standardised questionnaires administered by interviewers. Women aged 15-49 years were tested for HIV infection but children were not tested.

Outcome variable

The outcome variable is defined as a DTP3 vaccinated child of an HIV-infected mother with symptoms of acute respiratory infections or an episode of diarrhoea two weeks prior to the survey. The vaccinees were within the 12-23 months age range at the time of the surveys and at that age they were expected to have taken most of the basic childhood vaccines as specified by each country.

DHS defined symptoms of acute respiratory infections as a cough associated with short and rapid breathing in an ill under-five child within the two weeks preceding the survey. Diarrhoea is characterised by loose and watery stools three or more times a day in children.

Determinant variables

Individual-level factors

Five measures of individual socio-economic position were considered in the model, namely: age of the mother, educational level, wealth index, employment status and place of residence. The age of the mother was in completed years (15 to 24, 25 to 34, 35 to 49); level of education as no formal

education, primary education, and secondary or higher education; wealth index as either poorer, middle and richest; and employment status as currently employed or unemployed.

Community-level factors

We included the following community-level factors in the model: neighbourhood poverty rate defined as the percentage of households that are below 20% of wealth index; illiteracy rate which is the percentage of women without formal education within the community; unemployment rate defined as the percentage of women who are currently unemployed within the community; and, place of residence which is either urban or rural. We also classified the rates as low or high.

Country-level factors

The study included the following country-level factors in the model: gross domestic product (GDP) per capita, adult literacy rate and health expenditure (Table 1). We obtained these data from the World Bank database.[12] The country-level variables were also categorised into either low or high classes in order to assess nonlinear effects and for easy interpretation of results for policy decision making.

Statistical analyses

The distribution of respondents by various key variables were expressed as percentages. Pearson's chi-squared test was used for analysing contingency tables. We used individual weights for the descriptive statistics reported by this study. Multivariable logistic regression models were used to analyse the association between individual and contextual factors associated with symptoms of acute respiratory infections or diarrhoea among the children of women living with HIV and with the history of uptake of DTP3 vaccines.

We used a five-level model for the binary variable, namely:

First model: empty null model, an unconditional model without any explanatory variables.

Second model: for only individual-level factors.

Third model: for only community-level factors.

Fourth model: for only country-level factors.

Fifth model (Full model): that controlled for individual-, community- and country-level factors simultaneously (Figure 1).

The fixed-effects model results were presented as odds ratio (ORs) with 95% credible intervals (CrIs). The random effects measures included intra-cluster correlation (ICC) and variance partition coefficient and median odds ratio (MOR). We calculated ICC by the use of formula described by Snijders and Bosker.[13] The method used for the calculation of MOR was described by Larsen et al.[14,15] All the included tests were two tailed with the probability level of less than 0.05 considered to be significant. The models were fitted with MLwiN 3.01.[16] Statistical analysis were performed with the use of STATA 14.0.[17]

Ethics statement

This research was a secondary analysis of existing survey data which were obtained with permission from the DHS programme database.[11] These surveys were conducted after ethics approval by the Institutional Review Board of ICF International, Calverton, Maryland, USA and by respective National Ethical Review Committees in Angola, Burkina Faso, Burundi, Cameroon, Chad, the Democratic Republic of the Congo, Cote d'Ivoire, Ethiopia, Gabon, Gambia, Ghana, Guinea, Kenya, Lesotho, Liberia, Malawi, Mali, Namibia, Niger, Rwanda, Sao Tome and Principle, Senegal, Sierra Leone, Swaziland, Togo, Zambia and Zimbabwe. The study participants gave informed consent at the time of the surveys and their confidentiality was respected.

Results

Sample characteristics

The country surveys were conducted between 2003 and 2016 in the included countries (Table 1). Adult literacy rate in the included countries ranged from 15.5% in Niger to 90.1% in Sao Tome and Principe. The health expenditure per capita ranged from US$19.1 in Niger to US$321.3 in Gabon. GDP per capita data show that Gabon and Namibia are upper middle-income countries while eight other countries namely; Angola, Cameroon, Cote d'Ivoire, Ghana, Kenya, Senegal, Swaziland and Zambia are lower middle-income countries and the rest are low-income countries.

Table 2 shows the summary of symptoms of acute respiratory infections and episodes of diarrhoea among the children of HIV-infected mothers vaccinated with DTP3 at different levels in this study. For the summary of symptoms of acute respiratory infections, a total of 1,482 children aged 12-23

months (Level 1), within 1076 communities (Level 2), from 26 countries (Level 3) in sub-Saharan Africa were included. For the episodes of diarrhoea, a total of 4,027 children aged 12-23 months (Level 1), within 2267 communities (Level 2), from 27 countries (Level 3) in sub-Saharan Africa. Male and female children of HIV-infected women were evenly distributed. An estimated half of the included mothers were aged between 25 and 34 years, about three-fifths were not employed and two-fifths were in the richer wealth-index group. Most of the respondents were living in rural areas, within low poverty-rate and low literacy-rate groups.

Acute respiratory infections

Measures of associations (fixed effects)

Table 3 shows the multilevel multivariate logistic-regression models of the factors associated with symptoms of acute respiratory infections by children of HIV-infected women. At the community-level, the odds of developing symptoms of acute respiratory infections increased among those living in communities with high unemployment rates such that the children were 15% more likely to develop acute respiratory infections (odds ratio [OR] = 1.15, 95% credible interval [CrI] 1.05 to 1.26).

Measures of variations (random effects)

In model 1 (unconditional model), there was a significant variation in the odds of developing symptoms of acute respiratory infections among the children of HIV-infected mothers across the countries (σ^2 = 0.763, 95% CrI 0.359 to 1.514) and across the communities (σ^2 = 0.002, 95% CrI 0.001 - 0.006) (as shown in Table 3). The intra-country and intra-community correlation coefficients show that 18.81% and 18.85% of the variance in odds of developing symptoms of acute respiratory infections are linked to country- and community-level factors respectively. From the full model (Model 5), it is assumed that a child who moved to another country or community with a higher probability of developing symptoms of acute respiratory infections, the median increase in the odds of developing symptoms of acute respiratory infections would be 20.92% and 21.00% respectively.

Episodes of diarrhoea

Measures of associations (fixed effects)

Table 4 shows the multilevel multivariate logistic-regression models of the factors associated with episodes of diarrhoea by children of HIV-infected women. At the individual level, the odds of developing diarrhoea increased among young mothers such that children of women aged 15-24 years were twice as likely to develop diarrhoea compared to children of women aged 35-49 years (OR= 2.22, 95% Crl 1.66 to 2.93).

Measures of variations (random effects)

In model 1, there was a significant variation in the odds of developing diarrhoea among the children of HIV-infected mothers across the countries (σ^2 = 0.223, 95% CrI 0.058 to 0.532) and across the communities (σ^2 = 0.744, 95% CrI 0.302- 1.273) (as shown in Table 4). The intra-country and intra-community correlation coefficients show that 5.23% and 22.71% of the variance in odds of developing diarrhoea are linked to country- and community-level factors respectively. The variance in odds of not developing diarrhoea was also attributable to the country- and community-level factors respectively. From the full model (Model 5), it is assumed that a child who moved to another country or community with a higher probability of developing diarrhoea, the median increase in the odds of developing diarrhoea would be 5.63% and 26.73% respectively.

Table 1: Year of DHS survey and country level characteristics of 27 study countries in sub-Saharan Africa

Country	Year of survey	GDP per capita	Adult literacy rate	Health expenditure
Angola	2016	3110.8	66	179.4
Burkina Faso	2010	649.7	34.6	35.2
Burundi	2011	285.7	61.6	21.6
Cameroon	2011	1032.6	71.3	58.7
Chad	2015	664.3	22.3	37.1
Congo DR	2014	444.5	77	19.1
Cote d'Ivoire	2012	1526.2	43.9	88.4
Ethiopia	2003	706.8	39	26.6
Gabon	2012	7179.3	82.3	321.3
Gambia	2013	473.2	42	30.7
Ghana	2014	1513.5	71.5	57.9
Guinea	2012	508.1	32	37.3
Kenya	2009	1455.4	78.7	77.7
Lesotho	2014	998.1	76.6	105.1
Liberia	2013	455.4	42.9	46.3
Malawi	2016	300.8	62.1	29
Mali	2013	780.5	33.1	47.8
Namibia	2012	4140.5	88.3	499
Niger	2013	363.2	15.5	24.4
Rwanda	2015	702.8	68.3	52.5
Sao T&P	2009	1756.1	90.1	165.6
Senegal	2011	958.1	42.8	49.5
Sierra Leone	2013	496	32.4	85.9
Swaziland	2007	2775.2	83.1	247.9
Togo	2014	578.5	63.8	33.9
Zambia	2014	1178.4	83	85.9
Zimbabwe	2015	1008.6	88.7	57.7

GDP: gross domestic product, HDI: human development index, n/a: not available)
GDP - Low-income economies are defined as those with a GDP per capita of $1,025 or less; lower middle-income economies: $1,026 - $4,035; upper middle-income economies: $4,036 - $12,475; high-income economies: ≥ $12,476. HDI - low: <0.549; medium: 0.550 – 0.770.
(Source: Demographic and Health Surveys, World Bank, Joint United Nations Programme on HIV/AIDS, United Nations Development Programme)

Table 2: Summary of symptoms of acute respiratory infections and episodes of diarrhoea among the children of HIV-infected mothers with DTP3 uptake at different levels

	Symptoms of acute respiratory infections			Episodes of diarrhoea		
Variables	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
Individual-level factors						
Gender						
Female	533 (50.6)	196 (45.9)	0.104	1,663 (49.4)	324 (49.0)	0.855
Male	521 (49.4)	231 (54.1)		1,703 (50.6)	337 (51.0)	
Age (in years)						
15-24	269 (25.5)	115 (26.9)	0.592	751 (22.3)	197 (29.8)	0.000
25-34	512 (48.6)	212 (49.7)		1,706 (50.7)	333 (50.4)	
35-49	273 (25.9)	100 (23.4)		909 (27.0)	131 (19.8)	
Education						
No education	74 (7.0)	62 (14.5)	0.000	451 (13.4)	78 (11.8)	0.072
Primary	479 (45.5)	175 (41.0)		1,448 (43.0)	316 (47.8)	
Secondary+	501 (47.5)	190 (44.5)		1,467 (43.6)	267 (40.4)	
Employment status						
Unemployed	636 (60.3)	270 (63.2)	0.301	2,115 (62.8)	425 (64.3)	0.476
Employed	418 (39.7)	157 (36.8)		1,251 (37.2)	236 (35.7)	
Wealth index						
Poorer	325 (30.8)	126 (29.5)	0.842	893 (26.5)	197 (29.8)	0.165
Middle	305 (28.9)	129 (30.2)		996 (29.6)	196 (29.7)	
Richer	424 (40.3)	172 (40.3)		1,477 (43.9)	268 (40.5)	
Access to media						
Nil	298 (28.3)	92 (21.5)	0.035	715 (21.3)	162 (24.5)	0.195
Access to 1 outlet	309 (29.3)	139 (32.6)		1,041 (30.9)	290 (31.6)	
Access to 2 outlets	289 (27.4)	117 (27.4)		991 (29.4)	181 (27.4)	
Access to all outlets	158 (15.0)	96 (18.5)		619 (18.4)	109 (16.5)	
Community-level factors						
Place of residence						
Urban	444 (42.1)	166 (38.9)	0.250	1,494 (44.4)	283 (42.8)	0.457
Rural	610 (57.9)	261 (61.1)		1,872 (55.6)	378 (57.2)	
Poverty rate						
Low	625 (59.3)	258 (60.4)	0.690	2,103 (62.5)	391 (59.2)	0.107
High	429 (40.7)	169 (39.6)		1,263 (37.5)	270 (40.8)	
Unemployment rate						
Low	526 (49.9)	194 (45.4)	0.119	1,723 (51.2)	329 (49.8)	0.506
High	528 (50.1)	233 (54.6)		1,643 (48.8)	332 (50.2)	
Illiteracy rate						
Low	744 (70.6)	271 (63.5)	0.008	2,264 (67.3)	424 (64.2)	0.120
High	310 (29.4)	156 (36.5)		1,102 (32.7)	237 (35.8)	

Table 3: Factors associated with symptoms of acute respiratory infections by children of HIV-infected women identified by multilevel multivariate logistic-regression models

	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 5[e]
	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)
Fixed-effect					
Individual-effect factors					
Male (vs. female)		1.23 (0.95 -1.58)			1.22 (0.94 - 1.57)
Mother's age (in years)					
35-49		1 (reference)			1 (reference)
25-34		1.18 (0.86 - 1.58)			1.19 (0.86 - 1.59)
15-24		1.11 (0.76 - 1.54)			1.11 (0.75 - 1.58)
Wealth index					
Richer		1 (reference)			1 (reference)
Middle		1.10 (0.78 - 1.50)			1.00 (0.67 - 1.40)
Poorer		1.04 (0.71 - 1.48)			0.94 (0.56 - 1.43)
Education					
Secondary+		1 (reference)			1 (reference)
Primary		0.84 (0.62- 1.11)			0.83 (0.61 – 1.11)
No education		1.55 (0.95 – 2.37)			1.52 (0.88 - 2.43)
Not employment		1.02 (0.77 - 1.35)			0.84 (0.60 - 1.15)
Access to media		1.02 (0.88 - 1.18)			1.01 (0.88 - 1.19)
Community-level factors					
Rural (vs. urban)			1.26 (0.88 - 1.77)		1.35 (0.91 – 2.00)
High (vs. low) poverty rate			0.98 (0.87 - 1.10)		0.99 (0.87 - 1.12)
High (vs. low) unemployment rate			1.15 (1.05 - 1.26)*		1.17 (1.05 - 1.30)*
High (vs. low) illiteracy rate			1.01 (0.93 - 1.10)		0.98 (0.89 - 1.08)
Country-level factors					
Middle (vs. low) GDP				1.16 (0.40 – 2.52)	1.15 (0.36 – 2.90)
High (vs. low) Adult literacy rate				0.68 (0.27 - 1.37)	0.64 (0.21 - 1.44)
Average (vs. low) Health expenditure				1.06 (0.28 - 3.11)	1.23 (0.24 - 3.19)
Random effects					
Country-level					
Variance (95 CrI)	0.763 (0.359 – 1.514)	0.734 (0.341 – 1.460)	0.788 (0.359 – 1.578)	0.830 (0.363 - 1.691)	0.871 (0.378 – 1.792)
ICC (%)	18.81	18.21	19.27	20.13	20.92
MOR ((%, 95% CrI)	2.29	2.26	2.32	2.38	2.43
Explained variation (%)	Reference	3.7	-3.3	-8.8	-14.2
Community-level					
Variance (95 CrI)	0.002 (0.001 - 0.006)	0.008 (0.002 – 0.017)	0.012 (0.001-0.416)	0.001 (0.000 - 0.004)	0.003 (0.001 - 0.009)
ICC (%)	18.85	18.42	19.56	20.16	21.00
MOR ((%, 95% CrI)	1.04	1.09	1.11	1.03	1.05
Explained variation (%)	Reference	-380.2	-566.0	26.6	-79.4
Model fit statistics					
DIC	1550	1529	1548	1551	1556

DIC - Deviance Information Criterion; ICC – intra-cluster correlation; MOR – median odds ratio; OR- odds ratio; CrI – credible interval.
aModel 1 is a null model, baseline model without any determinant variable. bModel 2 is additionally adjusted for individual-level factors.
cModel 3 is additionally adjusted for community-level factors. dModel 4 is additionally adjusted for country-level factors.
eModel 5 is additionally adjusted for individual-, community-, and country-level factors

Table 4: Factors associated with episodes of diarrhoea by children of HIV-infected women identified by multilevel multivariate logistic-regression models

	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 5[e]
	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)
Fixed-effect					
Individual-effect factors					
Male (vs. female)		1.00 (0.83 -1.20)			1.01 (0.83 - 1.22)
Mother's age (in years)					
35-49		1 (reference)			1 (reference)
25-34		1.52 (1.15 – 1.95)*			1.58 (1.23 – 2.02)*
15-24		2.13 (1.57 – 2.80)*			2.22 (1.66 – 2.93)*
Wealth index					
Richer		1 (reference)			1 (reference)
Middle		1.05 (0.80 - 1.32)			1.04 (0.77 - 1.38)
Poorer		1.20 (0.90 - 1.58)			1.17 (0.82 - 1.66)
Education					
Secondary+		1 (reference)			1 (reference)
Primary		1.24 (0.98 - 1.57)			1.27 (0.98 - 1.57)
No education		0.94 (0.63 - 1.32)			0.90 (0.58 - 1.28)
Not employment		0.82 (0.66 – 1.00)			0.82 (0.65 - 1.03)
Access to media		0.97 (0.87 - 1.08)			1.00 (0.88 - 1.11)
Community-level factors					
Rural (vs. urban)			0.96 (0.73 - 1.24)		0.96 (0.69 - 1.29)
High (vs. low) poverty rate			1.05 (0.96 - 1.15)		1.02 (0.92 - 1.14)
High (vs. low) unemployment rate			0.98 (0.91 - 1.06)		1.00 (0.93 - 1.09)
High (vs. low) illiteracy rate			1.04 (0.97 - 1.13)		1.06 (0.98 - 1.15)
Country-level factors					
Middle (vs. low) GDP				0.91 (0.61 - 1.35)	0.89 (0.44 - 1.69)
High (vs. low) Adult literacy rate				1.29 (0.86 - 1.92)	1.32 (0.62 – 2.58)
Average (vs. low) Health expenditure				0.68 (0.42 - 1.08)	0.69 (0.34 - 1.27)
Random effects					
Country-level					
Variance (95 CrI)	0.223 (0.058 - 0.532)	0.241 (0.072 – 0.566)	0.229 (0.056 – 0.556)	0.083 (-0.010- 0.178)	0.253 (0.039 - 0.673)
ICC (%)	5.23	5.57	2.16	5.37	5.63
MOR ((%, 95% CrI)	1.57	1.59	1.32	1.58	1.61
Explained variation (%)	Reference	-8.3	62.4	-4.4	-13.5
Community-level					
Variance (95 CrI)	0.744 (0.302 – 1.273)	0.801 (0.437 - 0.122)	0.846 (0.510-1.246)	0.501 (0.251- 0.751)	0.947 (0.494 - 1.432)
ICC (%)	22.71	24.06	15.09	24.03	26.73
MOR ((%, 95% CrI)	2.27	2.34	1.96	2.35	2.52
Explained variation (%)	Reference	-7.7	32.7	-8.6	-27.3
Model fit statistics					
DIC	3501	3534	3494	3495	3470

DIC - Deviance Information Criterion; ICC – intra-cluster correlation; MOR – median odds ratio; OR- odds ratio; CrI – credible interval.
aModel 1 is a null model, baseline model without any determinant variable. bModel 2 is additionally adjusted for individual-level factors.
cModel 3 is additionally adjusted for community-level factors. dModel 4 is additionally adjusted for country-level factors.
eModel 5 is additionally adjusted for individual-, community-, and country-level factors

Discussion

Main findings

This study shows that the individual, community and country contexts are significant in explaining the variations in acute respiratory infections and diarrhoea among the children of HIV-infected mothers in the selected sub-Saharan African countries. Developing symptoms of acute respiratory infections are more likely in the children of HIV-infected women who live in communities with high unemployment rates. Our findings show that children of young HIV-infected women are more likely to develop diarrhoea than the children of older women in sub-Saharan African countries.

Communities with high unemployment rates have the characteristics of poor neighbourhoods such as poor housing, limited access to public services like healthcare, transportation, etc.[18] High-unemployment communities are linked with lower socio-economic status and are characterised by crowded rooms, poor nutrition, poor sanitation and unhygienic conditions.[19] Women living with HIV in these communities more or less belong to the lower socio-economic status.[20] Deprived neighbourhoods with high unemployment rates are associated with increased risk of mortality.[21] Cohen also shows that unemployment status is strongly associated with increased susceptibility to acute respiratory infection in humans due to reduced resistance to infection and increased exposure to infectious agents.[19] There is also a strong correlation between parental unemployment and children's poor health outcomes.[22]

Multinational research in developing countries located in Africa, the Americas, Asia and the Pacific shows the prevalence of acute respiratory infections among both HIV-infected and HIV-uninfected children to be 13%. The study also shows that factors like living in a high-risk indoor environment, male gender, employed mothers and low birthweight were positively associated with acute respiratory infections. Planned pregnancy, maternal education, older maternal age, breastfeeding for more than six months, and immunisation were associated with reductions in respiratory infections.[23]

Younger mothers are not as experienced as older women and are mostly learning to care for their first child.[24] The first child of adolescent and young mothers are most susceptible to both poor health outcomes and mortality.[24] The children of first–time, young mothers are at higher risk of developing diarrhoea, stunting and anaemia.[24] A multinational study on acute diarrhoea in developing countries among both immunised and non-immunised children shows that country inequalities, maternal illiteracy and unemployment were associated with diarrhoea.[25] Female children, normal birthweight, older children, complete immunisation coverage, advanced maternal age, planned pregnancy, good sanitation and rich households were associated with a reduction in episodes of diarrhoea.[25]

Furthermore, the findings from the multinational studies[23,25] involving children who were both immunised and unimmunised, HIV-exposed and non-exposed show an association with many factors while this multilevel analytic research included only HIV-exposed children who were vaccinated with DTP3 shows fewer associations.

Consistent, equitable availability and access to vaccination especially among the most vulnerable and poorest communities is essential in addressing non-uptake of basic vaccines in HIV-exposed children. The Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) which recommends an interrelated approach for the elimination of preventable diarrhea and pneumonia deaths has vaccination as one of the key interventions.[26] GAPPD brings together essential services and interventions such as promotion of practices that can protect children from these respiratory and diarrhoeal diseases and make sure that every child has access to suitable preventive measures and proper treatment.[27]

Strengths and limitations

The use of DHS gives this study a good quality and representation because the surveys were done in different regions of the included countries. However, this study has certain significant limitations. Firstly, the surveys were not conducted concurrently and within the same timeframe in each of the countries. Social conditions do change and are expected to change over time in these countries. The surveys were conducted in different countries over a time space of a decade and this may have some effect on the study findings. Secondly, DHS methodology being cross-

sectional, it does not give room for establishing causality. *Haemophilus Influenzae* type b (Hib) vaccine and rotavirus vaccine coverage as at 2016 were 74% and 43% among African countries. Pneumococcal vaccine global coverage was estimated at 42% in 2016.[27] The use of pneumococcal and rotavirus vaccination data would have provided added information with respect to independent contributions of various factors because, at the time when the surveys were conducted, most of the African countries were yet to introduce Hib, pneumococcal and rotavirus vaccines. Another gap in this study is the lack of information about the HIV status of the children.

Conclusions

This study gives insight concerning the determinants of key morbidity factors among immunised and HIV-exposed children in sub-Saharan Africa. The study reveals that residence in communities with high unemployment was an independent predictor of acute respiratory infections among immunised and HIV-exposed children. HIV-exposed children born to women aged 15-24 or 25-34 years old were significantly more likely to develop diarrhoeal diseases in sub-Saharan Africa.

These findings are important because they have policy implications on the implementation of child healthcare programmes for respiratory infections and diarrhoeal diseases particularly among HIV-exposed and infected children in sub-Saharan Africa. Public healthcare programmes should target adolescent and young women and their family members on how to prevent diarrhoea. Efforts should be made to identify the hotspots for acute respiratory diseases, especially in communities with high rates of unemployment, and to develop strategies to combat the diseases in such communities.

Further large data research is needed to study the effect of rotavirus, pneumococcal and Hib vaccines on the prevalence of diarrhoea and respiratory infection in sub-Saharan Africa populations. It is recommended that DHS should include the newer vaccines and HIV status for the children as part of the collected data so as to have a large database for a robust study of vaccine-preventable diseases in HIV-infected children across developing countries.

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome

ARV: Antiretroviral drugs

CrI: Credible interval

DHS: Demographic and health survey

DTP: Diphtheria-tetanus-pertussis

EPI: Expanded Programme on Immunization

GAPPD: Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea

GAVI: Global Alliance for Vaccines and Immunisation

GDP: Gross domestic product

HDI: Human Development Index

HIV: Human Immunodeficiency Virus

ICC: Intra-cluster correlation

MOR: Median odds ratio

OR: Odds ratio

PMTCT: Prevention of mother-to-child transmission

UNICEF: United Nations Children's Fund

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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Authors' contributions

OOA and OAU conceived the study. OOA did the data analysis, interpreted the results and wrote the initial manuscript. OAU and CSW reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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CHAPTER 8: Concluding remarks and recommendations for future work

Conclusion

This thesis provides an overview of the burden of vaccine-preventable diseases, efficacy and effectiveness of vaccines, vaccination coverage and contributory factors for non-uptake of vaccines among HIV-infected and HIV-exposed children in sub-Saharan Africa. This research determined the prevalence of symptoms of acute respiratory infections and episodes of diarrhoea; and assessed if there was any significant morbidity benefit conferred by vaccination. This study also examined the roles of the socio-economic factors in relation to vaccine uptake among HIV-infected and HIV-exposed children in sub-Saharan Africa.

The overall conclusions of this thesis are as follows:

i. The burden of vaccine-preventable diseases is still high among HIV-infected and HIV-exposed children in sub-Saharan Africa.
Methodology: Systematic review and meta-analysis.

ii. Several routine vaccines show possibilities for direct and indirect protection against various vaccine-preventable diseases among HIV-infected and HIV-exposed children. However, HIV-infected children are less likely to be protected against vaccine-preventable diseases compared to unexposed children. HIV-infected children who are on antiretroviral therapy and with good viral suppression are also more likely to be protected.
Methodology: Systematic review and meta-analysis.

iii. There is no significant difference in the uptake of the full series of three doses of diphtheria-tetanus-pertussis containing vaccines (DTP3) among infants of HIV-infected mothers and those of uninfected mothers in sub-Saharan Africa. However, there is a significant variation in terms of the estimates among the sub-Saharan African countries.
Methodology: Meta-analysis and meta-regression

iv. DTP3 coverage for both HIV-exposed children and non-exposed children is still sub-optimal. Improved prevention of mother-to-child transmission services might have contributed to some extent to the higher DTP3 vaccination coverage among the HIV-exposed children.
Methodology: Meta-analysis and meta-regression.

v. Individual and contextual factors such as maternal age, educational level, unemployment and adult literacy level contributed significantly to non-uptake of DTP3 among the children of HIV-infected women across sub-Saharan Africa.
Methodology: Multilevel multivariate regression modelling.

vi. The symptoms of acute respiratory infections show no statistical difference in the overall estimates between the children of HIV-infected mothers who were vaccinated with DTP3 and the ones who were not vaccinated. The data for episodes of diarrhoea were pooled together with resultant nil significant difference in the overall estimates between the children of HIV-infected mothers vaccinated with DTP3 and the ones that were not vaccinated. There was no significant difference in the overall estimates between the children of HIV-uninfected mothers who were vaccinated with DTP3 and those of mothers living with HIV with respect to the prevalence of symptoms of acute respiratory infections and episodes of diarrhoea across the study countries.
Methodology: Meta-analysis.

vii. Many African countries recorded high rates of respiratory infections and diarrhoeal diseases. This necessitates the need for accelerating the introduction of newer vaccines such as rotavirus, pneumococcal conjugate and *Heamophilus influenzae* type b vaccines in countries that are yet to introduce them as part of their national immunisation programme.
Methodology: Meta-analysis and meta-regression.

viii. Residence in communities with high unemployment was an independent predictor of acute respiratory infections among immunised and HIV-exposed children while those born to

women aged 15-24 or 25-34 years old were significantly more likely to develop diarrhoeal diseases in sub-Saharan Africa.

Methodology: Multilevel multivariate regression modelling.

Recommendations for future research

These findings are important because they have policy implications for the implementation of child healthcare programmes particularly among HIV-exposed and infected children in sub-Saharan Africa. These findings would be useful in advocating for an equitable share of healthcare resources for services like childhood vaccination etc.

This research also raises many issues that need to be investigated and I propose the following areas to be addressed in future research:

1. This thesis shows that there is a dearth of studies on the incidence, prevalence and case-fatality rates for various vaccine-preventable diseases among HIV-infected and HIV-exposed uninfected children in African countries. There is need for future studies that will showcase the real burden of vaccine-preventable diseases. The studies could be prospective or retrospective in nature. (Chapter 2).

2. There are few studies on vaccine efficacy and effectiveness specifically among HIV-infected and exposed children. There is a knowledge gap on vaccine efficacy and effectiveness of vaccines with a focus on HIV-infected and exposed children. Outcomes of interest for these studies should include the development of clinical features or laboratory confirmation of vaccine-preventable diseases (Chapter 3).

3. There is poorer vaccine efficacy among HIV-infected children and this necessitates the development of newer and more efficacious vaccines (Chapter 3).

4. There is a need for large data sets such as the demographic and health surveys to include new vaccines like rotavirus and pneumococcal conjugate vaccines. These are required to study the effects of these vaccines on the prevalence of diarrhoea and respiratory infections in sub-Saharan Africa populations. Future surveys should also include the

HIV status of the children as part of the collected data so as to have a large database for a robust study of vaccine-preventable diseases in HIV-infected and exposed children in African countries (Chapters 6 and 7).